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(54) Title: BENZIMIDAZOLONE ANTIVIRAL AGENTS

(57) Abstract: The present invention concerns antiviral compounds, their compositions, and use in the treatment of viral infections. More particularly, the invention provides benzimidazonone derivatives for the treatment of respiratory syncytial virus infection.

BENZIMIDAZOLONE ANTIVIRAL AGENTS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial Number 60/235,804 filed on September 27, 2000.

BACKGROUND OF THE INVENTION

1. Field of the Invention

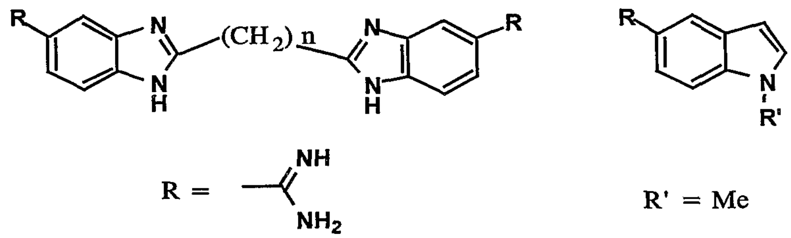
The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides benzimidazolone derivatives for the treatment of respiratory syncytial virus infection.

2. Background Art

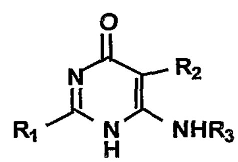
Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infection in infants, children, elderly and immunocompromised persons. Severe infection of the virus may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, *277*, 12). Currently only Ribavirin is approved for the treatment of this viral infection. Ribavirin is a nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. RespiGam, approved for prophylaxis in high risk pediatric patients, is an intravenous immunoglobulin which effectively neutralizes the virus. Recently, Synagis, a monoclonal antibody administered through intramuscular injection has also been approved for use in high risk pediatric patients. However, both drugs are very expensive. Accordingly, inexpensive, safe and effective antiviral agents against respiratory syncytial virus will be beneficial for patients.

Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, *7*, 193). Y. Tao et al. (EP 0 058 146 A1, 1998) disclosed that Ceterizine, a known antihistamine, exhibited anti-RSV activity. Tidwell et al., *J. Med. Chem.* 1983, *26*, 294 (US Patent 4,324,794, 1982), and Dubovi

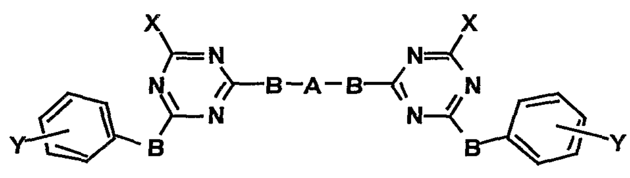
et al., *Antimicrobial Agents and Chemotherapy,* 1981, *19,* 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.



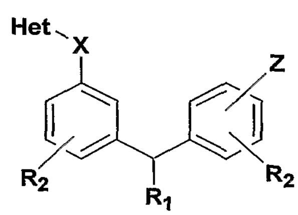
Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.



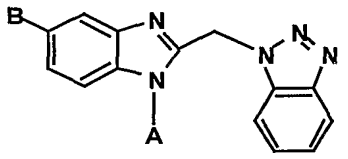
Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, *38,* 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or prevention of RSV infection.



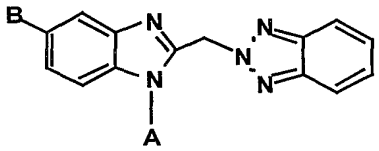
In addition, T. Nitz, et al., (WO Patent, WO 00/38508, 1999) disclosed a series of triaryl containing compounds that were useful for the treatment and/or prevention of RSV and related pneumoviral infections.



A related series of compounds were first disclosed by F. Pagani and F. Sparatore in *Boll Chim Farm.* 1965, *104,* 427 and by G. Paglietti, et al. in *Il Farmaco, Ed. Sci.* 1975, *30,* 505, and found to possess analgesic and anti-arrhythmic activity. The structural formula for these compounds are depicted in Formula Ia and Ib.

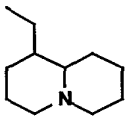


Formula Ia

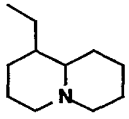


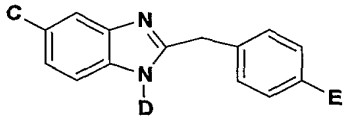
Formula Ib

In Formula Ia and Ib, A is $-(CH_2)n-N(R)_2$, n = 2 or 3, R = Me or Et,

or A is  ; B = H, Cl, CF_3, CH_3CO, NO_2.

Another series of closely related compounds that Sparatore had disclosed were in *Il Farmaco Ed. Sci.* 1967, *23,* 344 (US patent 3,394, 141, 1968). Some of the compounds were reported to have analgesic, anti-inflammatory or anti-pyretic activities. The structure of these compounds is depicted in formula Ic. In Formula Ic, C = H, CF_3, or NO_2. D is $-(CH_2)n-NR_2$, n = 2 or 3, R = Me or Et, or

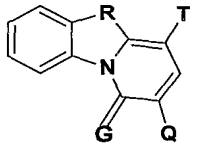
D =  ; E is H, Cl or OEt.



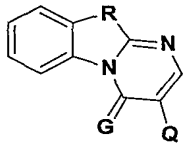
Formula 1c

Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, *3,* 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these compounds are shown in formulas Id and Ie, in which

R = NH, S, or O; Q = -NHCOPh, -COOH, COOEt, or CN; T = COMe, CN, or COOEt; G = O or NH.

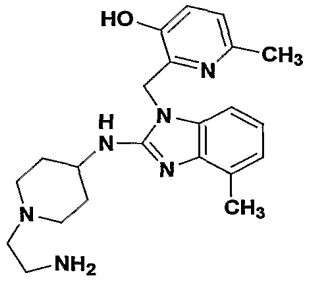


Formula 1d

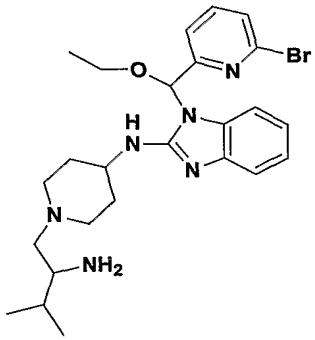


Formula 1e

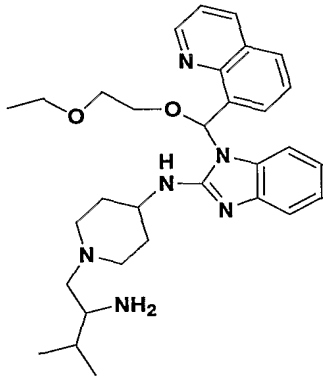
Another series of 2-aminobenzimidazoles have been reported by E. Janssens, et al. as inhibitors of RSV in a series of recent publications and representative examples formula 1f-1h are shown below from PCT WO 01/00611 A1; PCT WO 01/00612 and PCT WO 01/00615, respectively all published on January 4, 2001.



Formula 1f

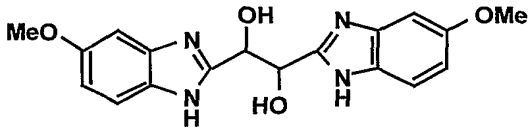


Formula 1g

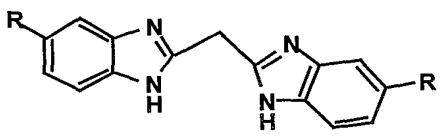


Forrnula 1h

A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, *15*, 655.

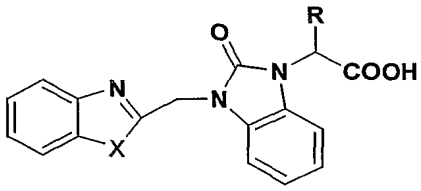


Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, *5*, 71.



R = H, NO_2

Also, H. R. Howard et al. reported a series of benzimidazolone-1-acetic acids that possessed aldolase reductase inhibitory activity (*Eur. J. Med. Chem.* 1992, *27*, 779-789).



X = O, S

Other prior art related to the chemical structure of the present invention:

(1) F. Sparatore, et al, "Derivati Benzotriazolici Attivi Sull'accrescimento Delle Piante," *Il Farmaco Ed. Sci.* 1978, *33*, 901.

(2) Katritzky, A. R. et al, "Synthesis and Transformations Of Substituted Benzazolyl- and Tetrazolyl(benzotriazol-l-yl)methanes," *J. Heterocyclic Chem.* 1996, *33*, 1107.

(3) Terri A. Fairley, et al. " Structure, DNA Minor Groove Binding, And Base Pair Specificity of Alkyl and Aryl-Linked Bis(amidinobenzimidazoles) and Bis(amidinoindoles), *J. Med. Chem.* 1993, *36*, 1746.

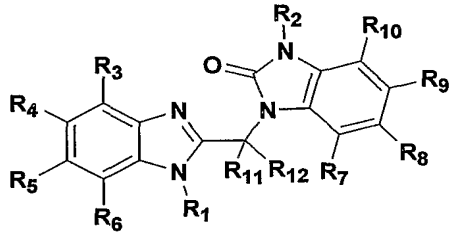
(4) R. K. Upadhyay et al, " New Synthesis and Biological Evaluation," *Indian J. Heterocyclic Chem.* 1994, *4*, 121.

(5) A. R. Katritzky, et al, " A New Route to N-substituted Heterocycles," *Tetrahedron*, 1993, *49*, 2829.

(6) K. Yu et al. in Substituted Benzimidazole Anti-viral Agents, PCT WO 00/04900 published February 3, 2000.

SUMMARY OF THE INVENTION

This invention relates to the antiviral activity against RSV found in a series of 1-substituted 2-(3'-N-substituted 2-oxo-benzimidazolylmethyl)-benzimidazoles. The structural formula for these compounds are depicted in Formula I, and includes pharmaceutically acceptable salts thereof.



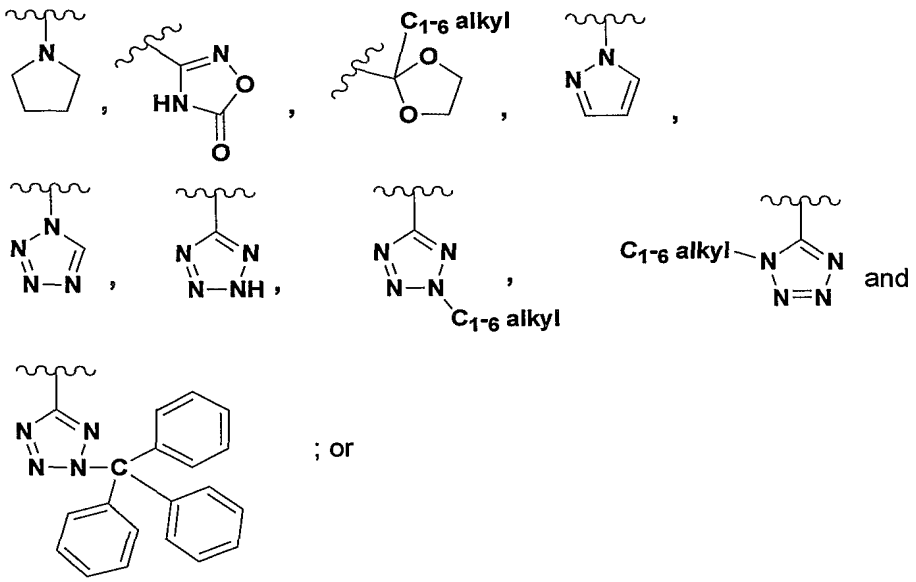
Formula I

wherein:

R_1 is $-(CR^vR^w)_n-X$;

R^v and R^w are independently selected from the group consisting of H, C_{1-6} alkyl, and C_{2-6} alkenyl; optionally substituted with 1-6 of the same or different halogen;

X is H, C_{1-6} alkyl, C_{2-6} alkenyl; each of said C_{1-6} alkyl, C_{2-6} alkenyl being optionally substituted with (1) one to six same or different halogen or hydroxy; (2) a member selected from the group consisting of phenyl, $-C(=NOH)NH_2$, $-CH(OH)-Ph$, $-Ph-S(O)_2C_{1-6}$ alkyl,



; or

(3) a member from Group A1;

Group A1 is CN, OR', NR'R", R'NCOR", NR'CONR"R"', NR'SO_2R", NR'COOR", COR', COOR', $OS(O)_2R'$, $S(O)_tR'$ or $PO(OR')_2$;

n is 1-6;

t is 0-2;

R_2 is

(i) H, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl, or a functionality selected from Group A2 or Group B; each of said C_{1-6} alkyl, C_{2-6} alkenyl, and phenyl being optionally substituted with (1) one to six same or different halogen or hydroxy or (2) one to two same or different members of Group A or Group B;

(ii) $-(CR^xR^y)_{n'}-(CO)_p-C_6H_4-(Z_1)(Z_2)$, wherein Z_1 and Z_2 are each independently selected from the group consisting of Group A, Group B, and $-(CH_2)_{n'}-Z'$; wherein said Z' is heterocycle or $-(NR_dR_eR_f)$ + (halogen)-; and the Z_1 and Z_2 groups may each be in the ortho, meta or para position relative to the $-(CR^xR^y)_{n'}-(CO)_p-$ group; wherein R_d, R_e and R_f are independently C_{1-6} alkyl, C_{2-6} alkenyl, OH or C_{1-6} alkyl COOH;

p is 0 or 1;

n' is 1-6; or

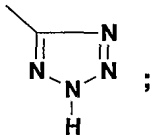
(iii) $-(CR^xR^y)_{n''}$-heterocycle;

n" is 0-6;

R_3, R_6, R_7 and R_{10} are each independently H;

R_5, R_8 and R_9 are each independently H, halogen or CF_3;

R_4 is selected from the group consisting of H, halogen, CN, $-C(O)C_{1-6}$ alkyl and


;

R_{11}, R_{12} are each independently H;

R^x, R^y are each independently H or C_{1-6} alkyl;

Group A2 is COR', COOR', CONR'R" or CONR'SO_2R";

Group A3 is CN, NO_2, OR', OCONR'R", NR'R", N(R') COR", N(R')CONR"R'", NR'SO_2R", NR'COOR", SO_mR', SO_2NR'R", SO_2NR'COR" or $PO(OR')_2$;

Group A is a member selected from Group A2 and Group A3;

R', R", R'" are each independently selected from the group consisting of H, C_{1-6} alkyl, phenyl and heterocycle; and each of said C_{1-6} alkyl, phenyl and heterocycle being optionally substituted with (1) one to six of same or different halogen or hydroxy; (2) one to two of the same or different members of Group A' or Group B; or (3) heterocycle; or R' and R" taken together form a 5 to 6 membered aromatic or non-aromatic ring containing one to four of the same or different heteroatoms selected from the group consisting of N, S and O;

Group A' is halogen, CN, NO_2, OR^a, $OCONR^aR^b$, NR^aR^b, R^aNCOR^b, $NR^aCONR^bR^c$, $NR^aSO_2R^b$, NR^aCOOR^b, COR', $CR^cNNR^aR^b$, CR^aNOR^b, $COOR^a$, $CONR^aR^b$, $CONR^aSO_2R^b$, $SO_{m'}R^a$, $SO_2NR^aR^b$, $SO_2NR^aCOR^b$ or $PO(OR^a)_2$;

R^a, R^b, R^c are each independently selected from the group consisting of H and C_{1-6} alkyl;

Group B is $-(CH_2)_{n'''}Q$, $-(CH_2)_{n'''}SO_{m''}-R_{13}$ or -COQ;

Q is an N-linked amino acid selected from the group consisting of alanine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, pipecolic acid, α-amino-butyric acid, α-amino-propanoic acid, 2-amino-3-phonopropionic acid and iminodiacetic acid; wherein Q is linked to the adjacent carbon atom in Group B through a nitrogen atom of said N-linked amino acid; wherein said N-linked amino acid includes D- or L-enantiomers or mixtures thereof;

R_{13} is selected from a group consisting of H and C_{1-6} alkyl; said C_{1-6} alkyl being optionally substituted with (1) one to five hydroxy groups or (2) two of the same or different functionalities selected from the group consisting of $COOR^x$ and $CONR^xR^y$;

m, m' and m'' are independently 0-2;

n''' is 1-6;

heterocycle is a 5-6 membered aromatic or non-aromatic ring which contains one to four heteroatoms independently selected from the group consisting of O, N and S; wherein said aromatic or non-aromatic ring is optionally fused to a phenyl ring; wherein the aromatic or non-aromatic ring is optionally substituted with one to five of the same or different substituents selected from the group consisting of C_{1-6} alkyl, Group A and Group B; and halogen is bromine, chlorine, fluorine or iodine.

In a preferred embodiment, the heterocycle is an aromatic ring selected from the group consisting of furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl,

pyrazinyl, 1,3,5-triazinyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, tetrazole, uridinyl and cytosinyl.

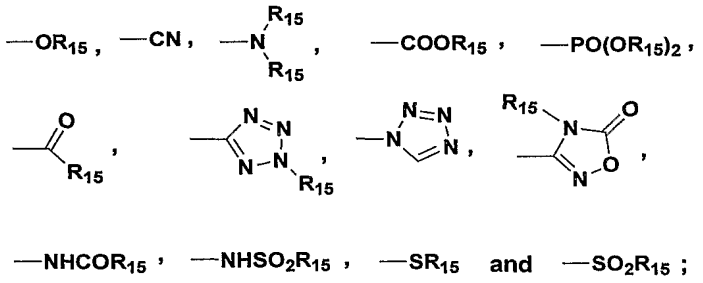
In another preferred embodiment, the heterocycle is a non-aromatic ring selected from the group consisting of pyrrolidine, imidazoline, 2-imidazolidone, 2-pyrrolidone, pyrrolin-2-one, tetrahydrofuran, 1,3-dioxolane, piperidine, tetrahydropyran, oxazoline, 1,3-dioxane, 1,4-piperazine, morpholine and thiomorpholine.

In another preferred embodiment in R_2, substituents R^x and R^y are each hydrogen. Also preferred is R_{11} and R_{12} each being hydrogen. Still more preferred are compounds wherein n' is 1 and n" is 3-4.

In another preferred embodiment, n is 1-4.

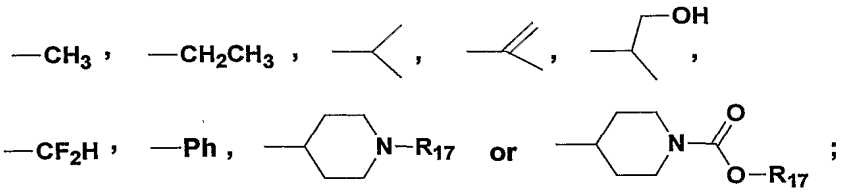
In another preferred embodiment are compounds wherein:

R_1 is vinyl, allyl, 3-methyl-2-butene or -(CH_2)n-X, wherein n is 2-4, and X is a functionality selected from the group consisting of



R_2 is

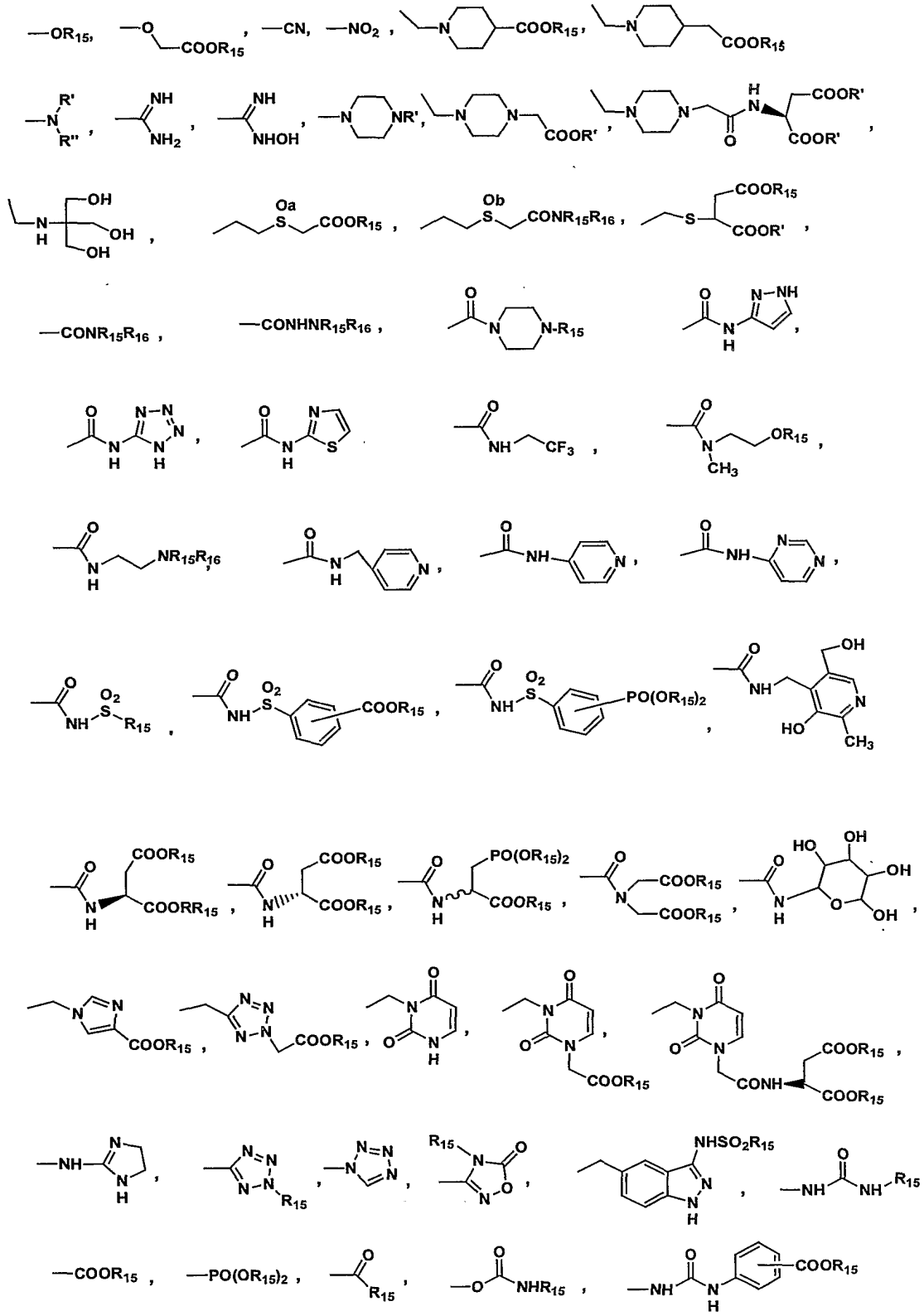
(i)



wherein R_{17} is H or C_{1-4} alkyl;

(ii) $-CH_2-C_6H_4-Z$;

(iii) $-(CH_2)_k-Z''$, wherein k is 1-6; wherein Z and Z'' are each independently selected from the group consisting of:



—NHCOR$_{15}$, —NHSO$_2$R$_{15}$, —NHSO$_2$CF$_3$, —SR$_{15}$, —SO$_2$R$_{15}$, —SO$_2$NR$_{15}$R$_{16}$ and —SO$_3$H;

a and b are each independently 0-2; and

R_{15} and R_{16} are each independently H, C_{1-4} alkyl, wherein said C_{1-4} alkyl is optionally substituted with 1-3 same or different halogens.

In another embodiment of the invention there is provided a method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds of having Formula I, including pharmaceutically acceptable salts thereof.

Another embodiment includes a pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned anti-RSV compounds of having Formula I, including pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

The term pharmaceutically aceptable salt includes solvates, hydrates, acid addition salts, base addition salts, and the salts of quarternary amines and pyridiniums. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic or organic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, acetic, citric, malonic, fumaric, maleic, sulfamic, or tartaric acids. The counter ion of quaternary amines and pyridiniums include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartrate. The base addition salts include but are not limited to salts such as sodium, potassium, calcium, lithium and magnesium.

Halogen means bromine, chlorine, iodine and fluorine.

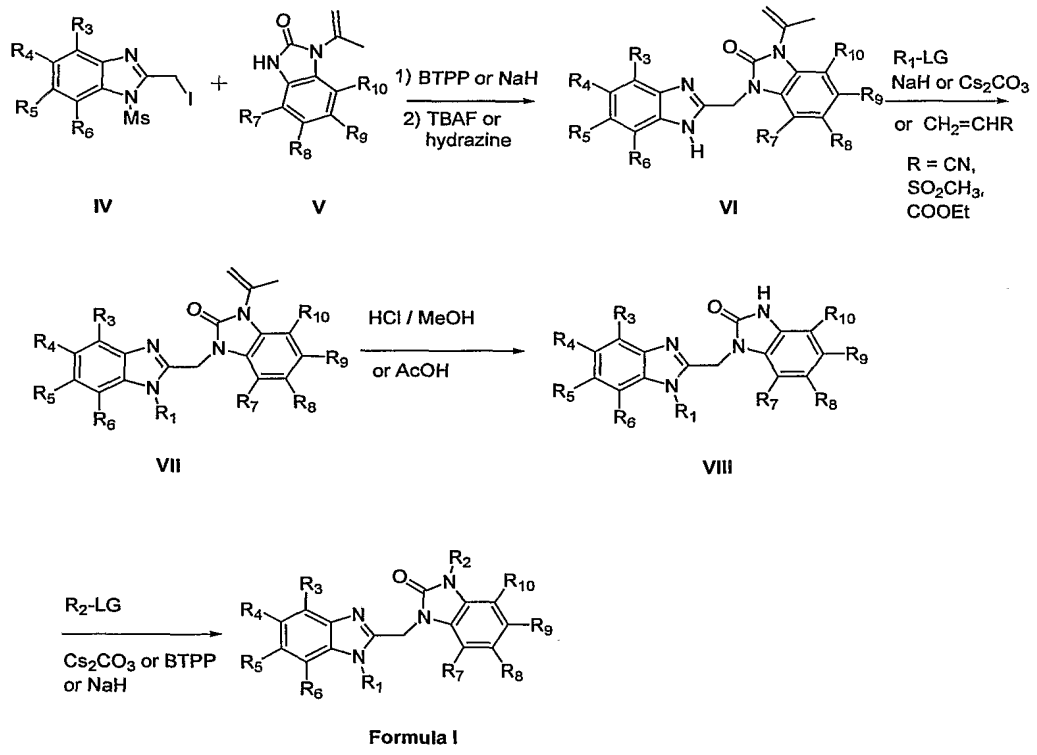
DETAILED DESCRIPTION OF THE INVENTION

Compounds of Formula **I** may be prepared using the procedures outlined in **Schemes I - V.**

Compounds of Formula **I** can be prepared as shown in **Scheme I.** Starting from the methansulfonamide of **IV**, alkylation with N-isopropylidenebenzimidazolone **V** in the presence of an appropriate base, such as NaH or a phosphazene base such as BTPP, followed by cleavage of the

methanesulfonamide with tetrabutylammonium fluoride (TBAF) gives compounds of Formula **VI**. Alkylation of compounds of Formula **VI** with R_1-LG where LG is a leaving group, preferably halide or sulfonate such as mesylate using an appropriate base such as NaH or Cs_2CO_3 provides compounds of Formula **VII**. Alternatively, compounds with Formula **VII** can be obtained through Michael addition of **VI** with acrylonitrile, vinyl sulfone, or an ester of acrylic acid. Alkylation of **VI** may give mixtures of regioisomers when R_3-R_6 are non-equivalent. These mixtures may be purified by various chromatographic techniques. Alternatively, single regioisomers can be obtained by employing a reaction sequence like that described in Scheme **IVa**. Cleavage of the isopropylidene moiety with acid such as hydrochloric acid or acetic acid followed by a second alkylation step with R_2-LG provides compounds of Formula **I**.

Scheme I

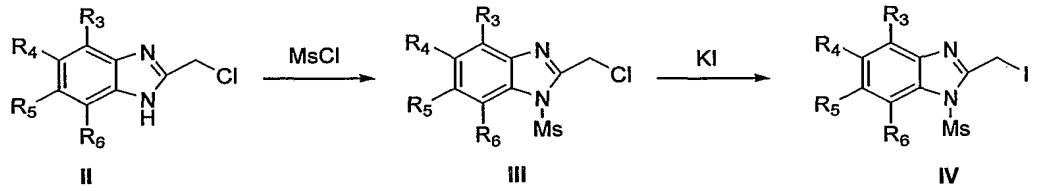


IV V VI VII VIII Formula I

Compound **IV** can be prepared using the reaction sequence depicted in **Scheme Ia**. When R4 and R5 are equivalent reaction of 2-chloromethylbenzimidazole (**II**) with methanesulfonyl chloride (MsCl) and

triethylamine gives compounds of Formula **III**. The chloride can be refluxed with potassium iodide in acetone to produce **IV**, as described in PCT WO 00/04900.

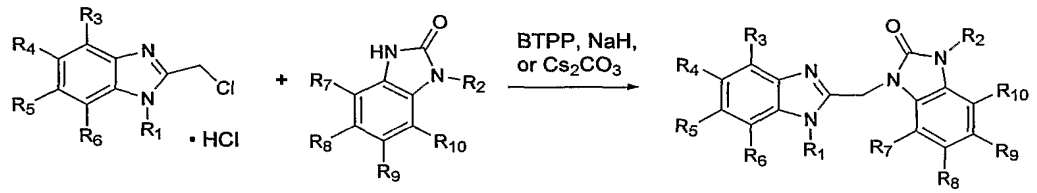
Scheme Ia



II III IV

Compounds of Formula **I** can also be prepared as shown in **Scheme II.** Alkylation of the substituted benzimidazolone of Formula **XIII** with a chloride **XI** in the presence of an appropriate base such as BTPP, Cs_2CO_3, or NaH, gives compounds of Formula **I**.

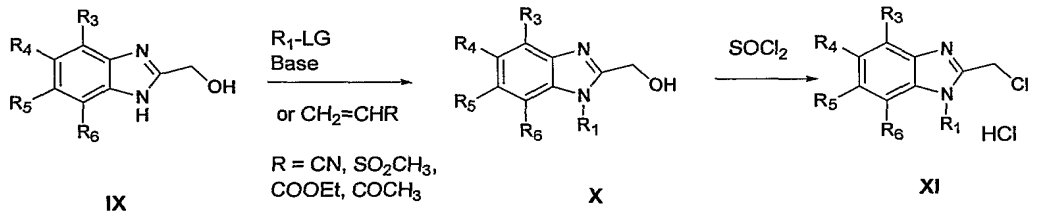
Scheme II



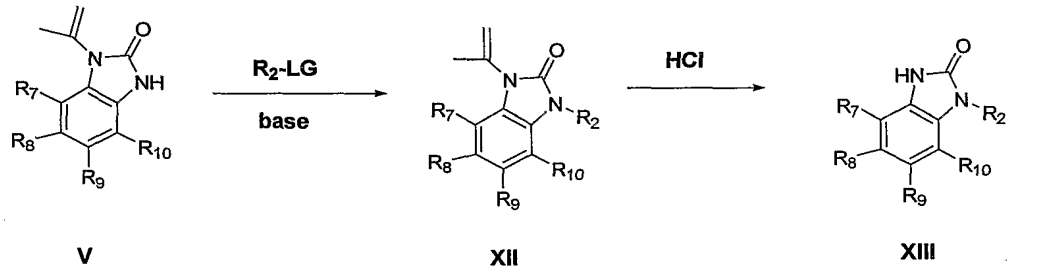
XI XIII Formula I

The synthesis of intermediates **XI** and **XIII** are depicted below in Schemes **IIa** and **IIb**, respectively. When R_4 and R_5 are equivalent selective N-alkylation of 2-hydroxybenzimidazole (**IX**) with R_1-LG or a Michael acceptor, such as acrylonitrile (R = CN), followed by conversion of the hydroxyl group of **X** to the chloride with $SOCl_2$ affords intermediate of Formula **XI**. Reaction of N-isopropylidenebenzimidazolone **V** with R_2-LG in the presence of an appropriate base such as NaH, BTPP, or Cs_2CO_3 affords intermediate **XII**. Cleavage of the isopropylidene moiety with acid gives compounds of Formula **XIII**.

Scheme IIa

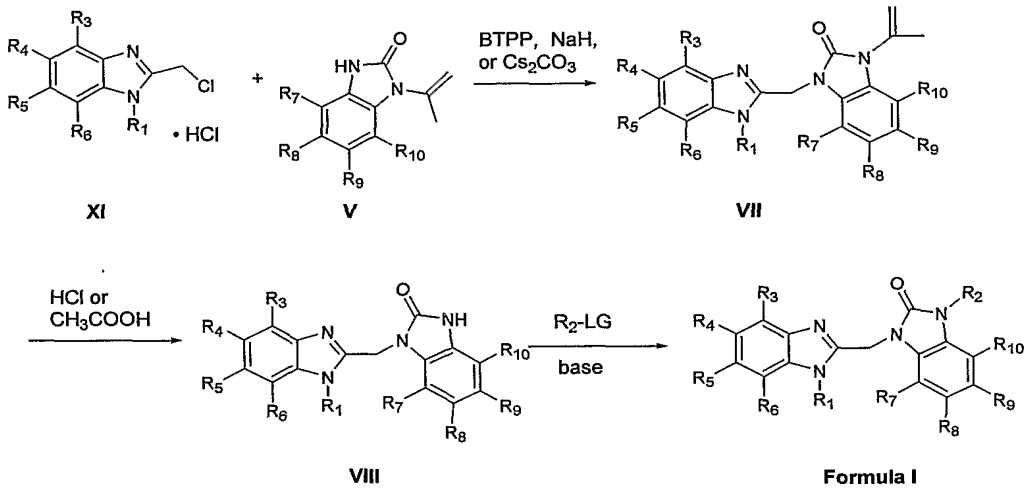


Scheme IIb



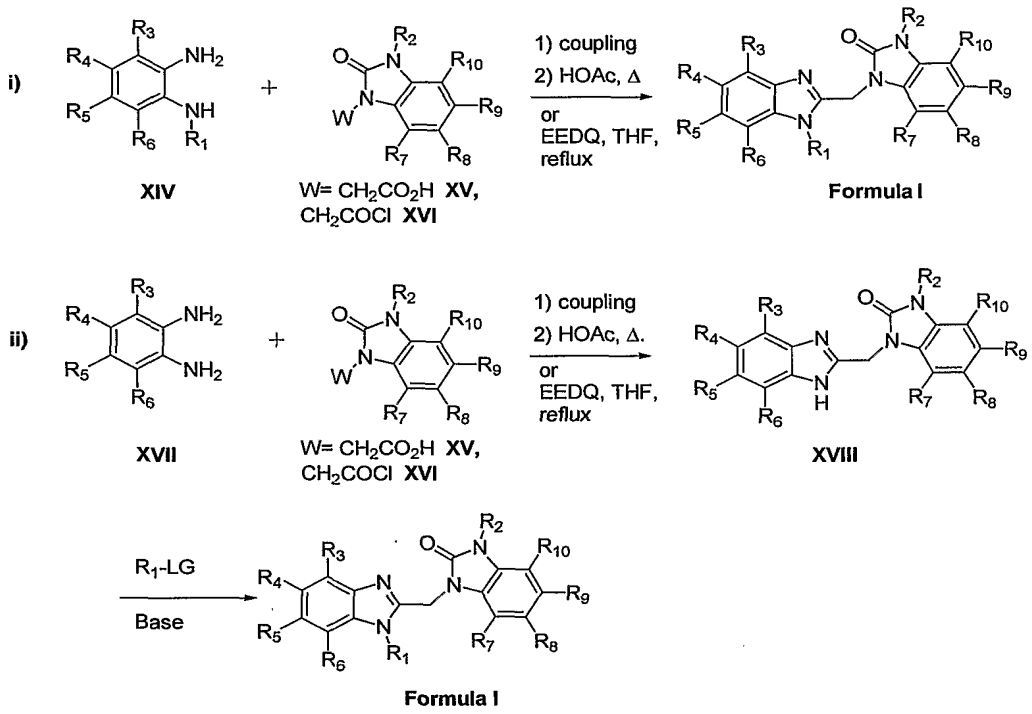
Additionally, a hybrid method from Schemes **I** and **II** may be employed for the preparation of compounds of Formula **I** as depicted in **Scheme III**. Coupling of intermediates **XI** and **V** in the presence of an appropriate base affords compounds of Formula **VII.** Cleavage of the isopropylidene moiety and reaction with R_2-LG utilizing the same procedures described in Scheme I gives compounds of Formula **I**

Scheme III



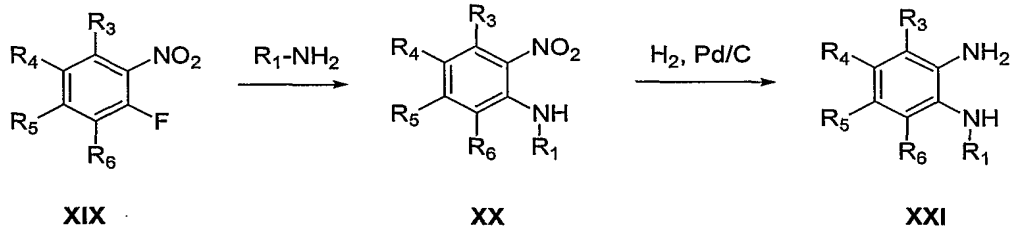
In a different approach, compounds of Formula **I** were prepared using the synthetic route illustrated in **Scheme IV**. Substituted phenylenediamine **XIV** can be coupled with either the acid **XV** through an amide coupling agent, such as a carbodiimide, or with the acid chloride **XVI** and a base. The crude material is directly cyclized to the benzimidazole in warm acetic acid to give compounds of Formula **I**. Alternatively, the phenylenediamine **XIV** can directly react with acid **XV** in the presence of EEDQ or the acid chloride **XVI** to give compounds of Formula **I**. In a slightly modified procedure depicted in **Scheme IV,** phenylenediamine **XIV** can be coupled with acid **XV** or acid chloride **XVI** in the same manner described above to give compounds of Formula **XXIII** which then can react with R_1-LG in the presence of an appropriate base to afford compounds of Formula **I**.

Scheme IV



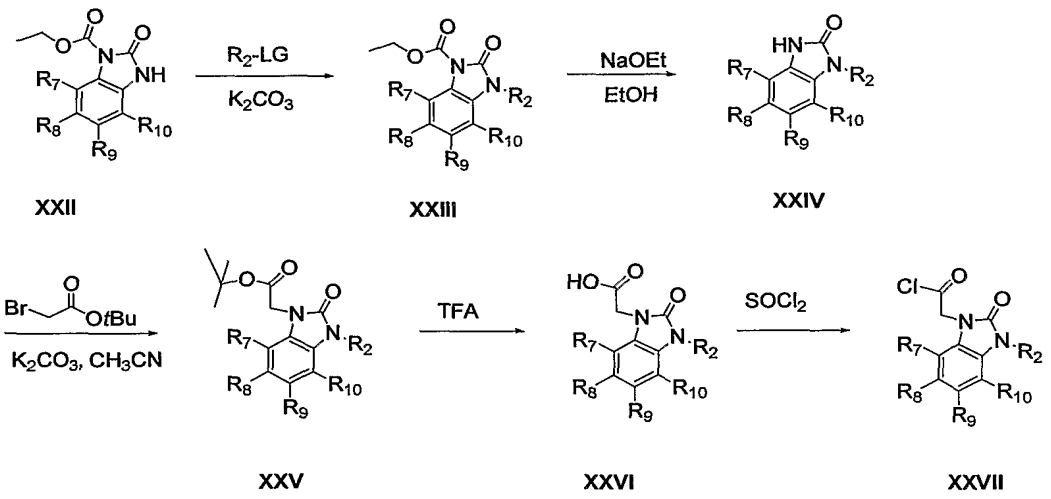
The preparation of pheneylenediamines **XXI** is described in **Scheme IVa**. Coupling of a 1-fluoro-2-nitrobenzene derivative **XIX** and the appropriate amine produces compounds of Formula **XX**. Reduction of compound **XX** under catalytic hydrogenation conditions to give phenylenediamine **XXI**.

Scheme IVa



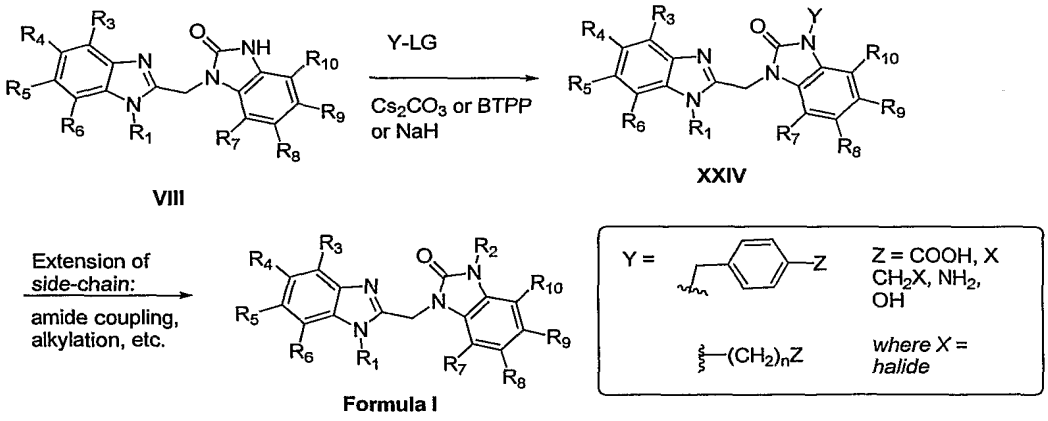
The right-hand benzimidazolone intermediates **XXI I** and **XXIII** can be prepared using standard alkylation chemistry and deprotection procedures as depicted in **Scheme IVb** starting with the known compound of Formula **XXII**.

Scheme IVb



Further modification of compounds at the R_2 side-chain can be accomplished by extension of the side-chain with one or more linkers as described in **Scheme V**. Alkylation of compounds of Formula **VIII** with a linker (Y-LG) in the presence of an appropriate base such as Cs_2CO_3, NaH, or BTPP affords intermediates **XXIV**. Intermediate **XXIV** is then extended through standard coupling and alkylation reactions to give compounds of Formula **I**.

Scheme V



Abbreviations used herein, including in Schemes I-V, experimental section unless indicated otherwise:

AcOH: acetic acid

AIBN: azobisisobutyronitrile

BEMP: 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorane
BTPP: *t*-butylimino-tri(pyrrolidino)phosphorane
DEAD: diethyl azodicarboxylate
DMF: dimethylformamide
EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EEDQ: 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
Et: ethyl
Et_2O: diethyl ether
EtOAc: ethyl acetate
EtOH: ethyl alcohol
HOAc: glacial acetic acid
Me: methyl
MeOH: methyl alcohol
MTBD: 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a] pyrimidine
Ph: phenyl
Prep HPLC: preparative high performance liquid chromatography
PyBroP: bromotripyrrolidinophosphonium hexafluorophosphate
TBAF: tetrabutylammonium fluoride
TEA: triethylamine
TFA: trifluoroacetic acid
THF: tetrahydrofuran
Tr: triphenylmethyl (trityl) group

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, a suitable dose will be in the range of from about 0.01 to 750 mg/kg of body weight per day preferably in the range of 0.1 to 100 mg/kg/day, most preferably in the range of 0.5 to 25 mg/kg/day.

Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However, the treatment can also be commenced when given post-infection, for example after the appearance of established symptoms.

Suitable treatment is to administer the compound 1-4 times daily and continue for 3-7 days, e.g. 5 days, post infection, depending upon the particular compound used.

The desired dose may be adminstered as a single dose or in divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form, for example, containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of the formula I, but not subject to the proviso thereto, or a pharmaceutically acceptable salt or derivative thereof together with a pharmaceutically acceptable carrier thereof.

The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical formulations may be in the form of conventional formulations for the intended mode of administration.

For intranasal administration according to the method of the invention the compounds of the invention may be administered by any of the methods and formulations employed in the art for intranasal administration.

Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder. Solid carriers include, for example, starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin.

Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water), or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, and polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients, for example, preservatives (such as benzalkonium chloride), solubilizing agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

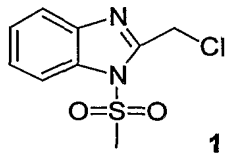
Intranasal administration may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluroroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Advance 500, AC-300, Bruker DPX-300 or a Varian Gemini 300

spectrometer. All spectra were determined in $CDCl_3$, CD_3OD, or DMSO-d_6 and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets; dt, doublet of triplets. Mass spectroscopy was performed on a Finnigan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes or on a LC-MS using Shimadzu LC-10AS with micromass platform LC single quadrupole mass spectrometer in positive electrospray ionization. High resolution mass spectroscopy was recorded using a Finnigan MAT 900. Infrared (IR) spectra were recorded on a Perkin-Elmer system 2000 FT-IR. Elemental analysis was performed with a Perkin-Elmer series II, model 2400 CHN/O/S analyzer. Column chromatography was performed on silica gel from VWR Scientific. Preparative HPLC was performed using a Shimadzu LC-8A on a C18 column eluted with mixture of MeOH in water with 0.1 % trifluoroacetic acid.

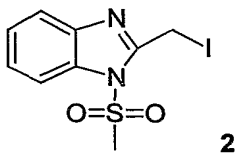
Preparation of Compounds as depicted in Scheme I:



1

To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in CH_2Cl_2 (0.5 L), triethylamine (136 mL, 0.97 mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated with MeOH and filtered to afford 74.9 g (64% yield) of compound **1** as a brown solid:

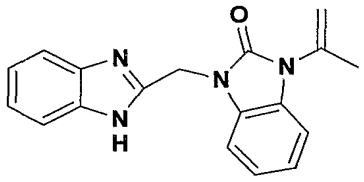
^1H NMR ($CDCl_3$) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m, 1 H), 7.85-7.91 (m, 1 H);
IR (KBr, cm^{-1}) 3027, 2920, 1371, 1349, 1177, 1144, 1059;
MS m/e 245 (MH^+);
Anal. Calcd for $C_9H_9ClN_2O_2S$: C, 44.18; H, 3.71; N, 11.45
Found: C, 44.09; H, 3.57; N, 11.49.



2

A solution of potassium iodide (206 g, 1.24 mol) and compound **1** (74.8 g, 0.414 mol) in acetone (1 L) was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in MeOH and filtered to give 83 g (60% yield) of compound **2** as a solid:

^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);
IR (KBr, cm^{-1}) 3022, 2916, 1366, 1173, 1055, 966, 763, 745;
MS m/e 336 (MH^+);
Anal. Calcd for $C_9H_9IN_2O_2S$: C, 32.16; H, 2.70; N, 8.33
Found: C, 32.05; H, 2.63; N, 8.22.

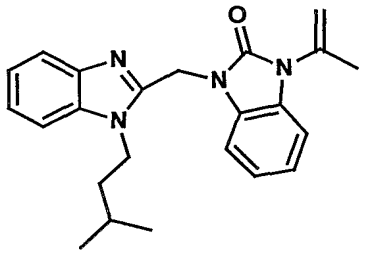


3

2-(Iodomethyl)-1-(methanesulfonyl) benzimidazole, **2**, (160 g, 0.476 mol) and 1-isopropenyl-2-benzimidazolone (prepared using the procedure described by J. Davoll, J. Chem. Soc. 1960, p308) were dissolved in 2 L of anhydrous THF and the solution cooled in a ice bath. To the solution, BTPP (223 g, 0.714 mol) was slowly added. The ice bath was removed, and the mixture was stirred at room temperature for 1.5 hours. The solution was evaporated. The residue was dissolved in ethyl acetate, washed with water, brine, dried over magnesium sulfate and evaporated. The residue was dissolved in THF (1 L) and tetrabutylammonium fluoride hydrate (130.7 g, 0.5 mol) was added. The mixture was stirred at reflux for 5 hours. The solvent was evaporated. The residue was dissolved in EtOAc, washed with water, brine, dried over magnesium sulfate, and evaporated. The residue was purified through a short silica gel column with EtOAc in CH_2Cl_2 (10 to 100%) to give 92.0 g (72% yield) of compound **3** as a solid:

^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 5.22 (s, 1H), 5.41 (s, 3H), 7.09-7.17 (m, 3H), 7.26-7.30 (m, 2H), 7.39 (d, J = 6.9 Hz, 1H), 7.60 (dd, J = 3.3, 6.0 Hz, 2H);
MS m/e 305 (MH^+).

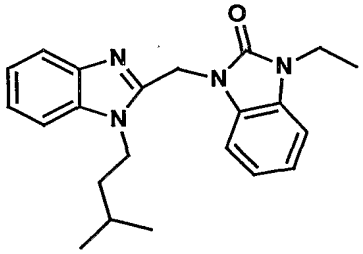
Compound 4 (Scheme I)



4

To compound **3** (30.4 g, 100 mmol) in DMF (200 mL) was added NaH (60% in mineral oil, 5.2 g, 130 mmol) in several portions at room temperature. After stirring for 30 minutes, 1-bromo-3-methylbutane (16.62 g, 110 mmol) was added to the suspension and the mixture was stirred at 70 °C overnight. The crude product was purified by flash chromatography to give 33.7 g (90% yield) of compound **4** as a white solid:

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6 H), 1.37-1.45 (m, 2 H), 1.64-1.75 (m, 1 H), 2.25 (s, 3 H), 4.31 (bt, J = 8.1Hz, 2 H), 5.21 (s, 1 H), 5.38 (s, 1 H), 5.40 (s, 2 H), 7.01-7.10 (m, 3 H), 7.25 -7.35 (m, 3 H), 7.46-7.47 (m, 1 H), 7.79-7.82 (m, 1 H);
IR (KBr, cm^{-1}) 2962, 1702, 1491, 1471, 1395, 1331, 740, 734;
MS m/e 375 (MH^+);
Anal. Calcd for $C_{23}H_{26}N_4O$: C, 73.77; H, 7.00; N, 14.96
Found: C, 73.82; H, 6.94; N, 14.91.

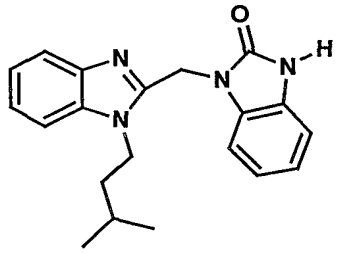


Compound 5 (Scheme I)

Compound **5** was prepared as described for compound **4** using 1-ethyl-1,3-dihydro-benzoimidazol-2-one.

^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 6H), 1.32-1.40 (m, 5H), 1.63-1.72 (m, 1H), 3.90-4.01 (m, 2H), 4.27-4.33 (m, 2H), 5.43 (s, 2H), 6.90-7.12 (m, 4H), 7.26-7.29 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.79-7.82 (m, 1H), 8.46 (bs, 1H);
MS m/e 363 (MH^+).

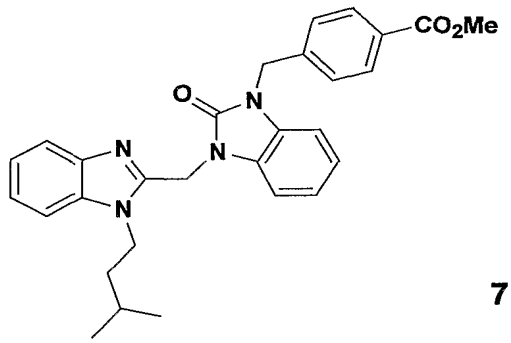
Compound 6 (Scheme I)



To compound **4** (33.7 g, 90 mmol) was added to 10% conc. HCl in MeOH (100 mL) and the reaction mixture was stirred at 75 °C for 1 h. The solvent was evaporated, and to the residue was added saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was passed through a short silica gel column to give a product which crystallized from CH_2Cl_2/EtOAc to give 22.83 g (84% yield) of compound **6** as white solid:

^{1}H NMR ($CDCl_3$) δ1.89 (d, J = 6.6 Hz, 6 H), 1.38-1.46 (m, 2 H), 1.67-1.74 (m, 1 H), 4.29-4.35 (m, 2 H), 5.46 (s, 2 H), 7.01-7.08 (m, 3 H), 7.28-7.31 (m, 3 H), 7.42-7.44 (m, 1 H), 7.81-7.84 (m, 1 H), 9.78 (bs, 1 H);
IR (KBr, cm^{-1}) 2957, 1696, 1489, 1458, 1390, 1332, 749, 737;
MS m/e 335 (MH^+);
Anal. Calcd for $C_{20}H_{22}N_4O$: C, 70.69; H, 6.70; N, 16.49
Found: C, 70.43; H, 6.69; N, 16.25.

Compound 7 (Scheme I)



7

A solution of compound **6** (212 mg, 0.63 mmol) and methyl 4-(bromomethyl)-benzoate (160 mg, 0.70 mmol) in THF (2 mL) was cooled to 0° and BTPP (219 mg, 0.7 mmol) was added dropwise under nitrogen. The resulting mixture was stirred at 0° for 0.5 h then at room temperature for 2 hours. The mixture was diluted with EtOAc and washed with water. The organic extracts were dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, hexanes:EtOAc 2:1 to 1:2) to give (219 mg, 71% yield) of compound **7** as a white solid:

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6 H), 1.47 (m, 2 H), 1.70 (m, 1 H), 3.91 (s, 3 H), 4.34 (m, 2 H), 5.16 (s, 2 H), 5.49 (s, 2 H), 6.82 (d, J = 8.9 Hz, 1 H), 7.02 (m, 2 H), 7.29 (m, 3 H), 7.38 (d, J = 8.3 Hz, 2 H), 7.50 (d, J = 7.3 Hz, 1 H), 7.82 (m, 1 H), 7.99 (d, J = 8.3 Hz, 2 H);

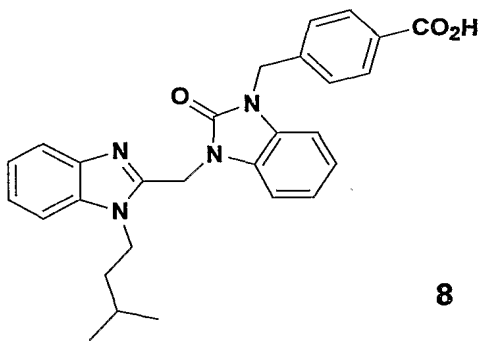
IR (KBr, cm^{-1}) 3418, 2952, 1707, 1495, 1406, 1279, 748;

MS m/e 483 (MH^+);

Anal. Calcd for $C_{29}H_{30}N_4O_3$: C, 72.18; H, 6.27; N, 11.61

Found: C, 71.95; H, 6.20; N, 11.41.

Compound 8

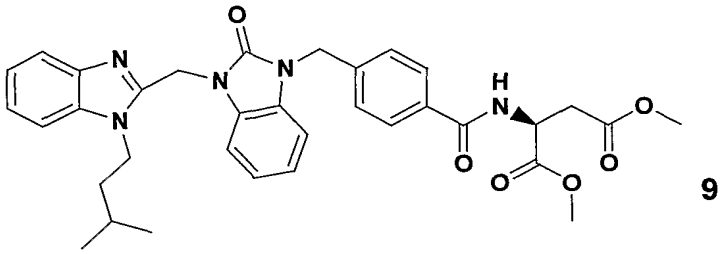


8

Compound **7** (130 mg, 0.27 mmol) was dissolved in methanol (2 mL). A solution of 1N NaOH (0.81 mL, 0.81 mmol) was added and the resulting mixture was heated to reflux for 3 h then cooled to room temperature. The solution was concentrated, and adjusted to pH 5 with 1N HCl. The precipitate was filtered and dried to give 81 mg (63% yield) of compound **8**. The acid was then converted to a sodium salt by adding aqueous $NaHCO_3$, and the resulting solution was adjusted to pH 8 with 1N HCl. The solution was evaporated to give the sodium salt of compound **8** as a white solid:

^{1}H NMR (DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.46 (m, 2 H), 1.65 (m, 1 H), 4.32 (m, 2 H), 5.09 (s, 2 H), 5.42 (s, 2 H), 6.99 (m, 2 H), 7.10 (m, 1 H), 7.29 (m, 5 H), 7.51 (d, J = 7.3 Hz, 1 H), 7.60 (d, J = 7.3 Hz, 1 H), 7.78 (d, J = 8.3 Hz, 2 H);
IR (KBr, cm^{-1}) 3396, 2956, 1703, 1612, 1598, 1329, 750;
MS m/e 469 (MH^+);
Anal. Calcd for $C_{28}H_{27}N_4O_3Na \cdot 1.5NaCl \cdot 2H_2O$: C, 54.79; H, 5.09; N, 9.12
Found: C, 55.08; H, 5.35; N, 8.86.

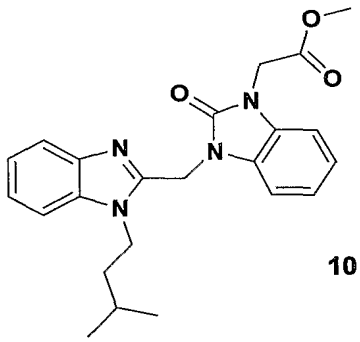
Compound 9



9

To a suspension of acid **8** (6.80 g, 14.5 mmol) in DMF (200 mL) at 0 ^{0}C was added PyBroP (7.41 g, 15.9 mmol). The suspension was stirred at 0 °C until it turned to a clear solution (about 30 minutes). Diisopropylethylamine (7.49 g, 57.9 mmol) and (L)-aspartic acid dimethyl ester hydrochloride (3.14 g, 15.9 mmol) were added and the resulting solution was stirred at ambient temperature overnight. The solvent was evaporated and the residue was purified by column chromatography (hexane : EtOAc 3:1 to1:4) to afford 8.30 g (94% yield) of compound **9** as a white solid:

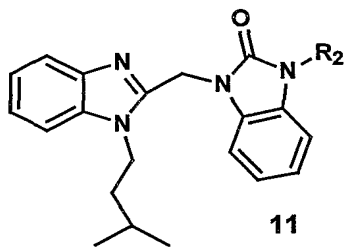
^{1}HNMR (DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6H), 1.41-1.48 (m, 2H), 1.59-1.68 (m, 1H), 2.72-2.97 (m, 2H), 3.57(s, 3H), 3.61 (s, 3H), 4.29 (t, J = 7.9 Hz, 2H), 4.76-4.83 (m, 1H), 5.17 (s, 2 H), 5.42 (s, 2H), 6.98-7.25 (m, 6H), 7.44 (d, J = 8.3 Hz, 2H), 7.50(d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.3 Hz, 1 H), 7.78 (d, J = 8.3 Hz, 2H), 8.88 (d, J = 7.7 Hz, 1H);
IR (KBr, cm^{-1}) 3312, 2953, 1740, 1708, 1495, 1170, 846, 748;
MS m/e 612 (MH^+);



10

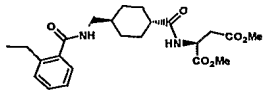
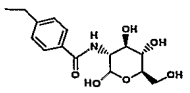
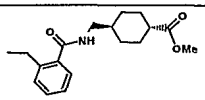
Compound **10** was prepared as described for compound **7** using methyl bromoacetate and sodium hydride as the base.

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.42-1.56 (m, 2H), 1.64-1.73 (m, 1H), 3.76 (s, 3H), 4.29 (t, J = 8.2 Hz, 2H), 4.66 (s, 2H), 5.44 (s, 2H), 6.84-6.90 (m, 1H), 7.04-7.10 (m, 3H), 7.27-7.30 (m, 2H), 7.44-7.52 (m, 1H), 7.76-7.82 (m, 1H);
MS m/e 406 (MH^+).

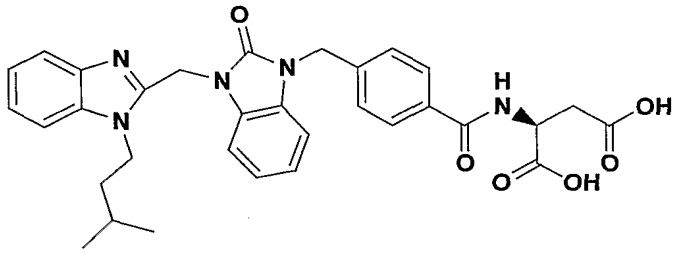


11

Table 1 – Additional examples prepared as described for compound **9**.

#	R_2	^{1}H-NMR Data	MS Data
11a		($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 6H), 0.99-1.13 (m, 2H), 1.43-1.51 (m, 4H), 1.56-1.69 (m, 2H), 1.84-1.98 (m, 4H), 2.00-2.16 (m, 1H), 2.80-3.08 (m, 2H), 3.28 (t, J = 6.3 Hz, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 4.29 (t, J = 8.2 Hz, 2H), 4.83-4.89 (m, 1H), 5.30 (s, 2H), 5.45 (s, 2H), 6.50 (d, J = 8.1 Hz, 1H), 6.90-6.96 (m, 1H), 7.06-7.09 (m, 2H), 7.21-7.24 (m, 1H), 7.31-7.34 (m, 4H), 7.43-7.50 (m, 2H), 7.75-7.78 (m, 1H)	751 (MH^+)
11b		($DMSO-d_6$) δ 0.91 (d, J = 6.5 Hz, 6H), 1.47-1.54 (m, 2H), 1.64-1.70 (m, 1H), 1.73-1.77 (m, 1H), 3.07-3.19 (m, 2H), 3.45-3.51 (m, 2H), 3.57-3.66 (m, 2H), 3.70-3.79 (m, 2H), 4.38 (t, J = 8.1 Hz, 2H), 4.58 (d, J = 8.3 Hz, 2H), 5.04 (d, J = 3.0 Hz, 1H), 5.17 (s, 2H), 5.51 (s, 2H), 7.00-7.03 (m, 2H), 7.08-7.13 (m, 1H), 7.25-7..36 (m, 3H), 7.42 (d, J = 8.4 Hz, 2H), 7.63 (t, J = 6.7 Hz, 2H), 7.80 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 7.2 Hz, 1H)	630 (MH^+)
11c		($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 6H), 1.03-1.14 (m, 2H), 1.39-1.66 (m, 7H), 1.91-2.06 (m, 4H), 2.24-2.33 (m, 1H), 3.35 (t, J = 6.4 Hz, 2H), 3.68 (s, 3H), 4.27-4.34 (m, 2H), 5.32 (s, 2H), 5.52 (bs, 2H), 7.00-7.13 (m, 4H), 7.16-7.19 (m, 1H), 7.30-7.35 (m, 4H), 7.49-7.62 (m, 2H), 7.82-7.87 (m, 1H)	622 (MH^+)

Compound 12



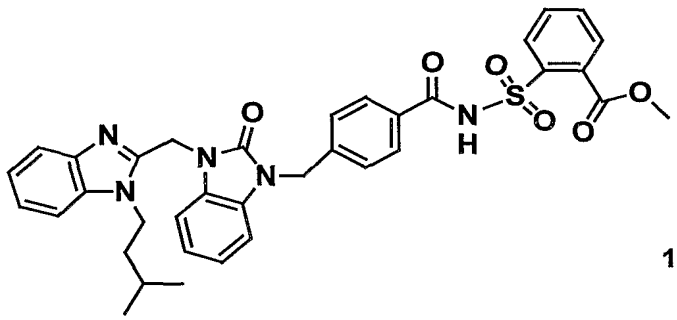
12

To a solution of compound **9** (3.3 g, 5.39 mmol) in MeOH (100 mL) was added 1 N NaOH (32 mL) and the solution was stirred at 60 °C for 10 min. The solvent was evaporated. The residue was dissolved in water and adjusted to pH 2

with 1N HCl, extracted with THF and then EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was triturated in EtOAc to give 2.55 g of compound **12** as a free acid. To the acid in methanol (50 mL) was added 2 equivalents of 1 N NaOH and solvent was evaporated. The residue was triturated with Et_2O to give 2.53 g of the disodium salt of compound **12** as a white solid:

^{1}H NMR (CD_3OD) δ 0.95 (d, J = 6.6 Hz, 6 H), 1.43-1.51 (m, 2 H), 1.64-1.73 (m, 1 H), 2.82 (d, J = 5.9 Hz, 2 H), 4.35-4.40 (m, 2 H), 4.70 (t, J = 5.9 Hz, 1 H), 5.24 (s, 2 H), 5.51 (s, 2 H), 7.02 -7.06 (m, 3 H), 7.18-7.36 (m, 3 H), 7.45-7.51 (m, 3 H), 7.67 (dd, J = 1.7, 7.0 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 2 H);
IR (KBr, cm^{-1}): 3411, 2956, 1706, 1612, 1494, 1407, 854, 749;
MS m/e 584 (MH^+).

Compound 13



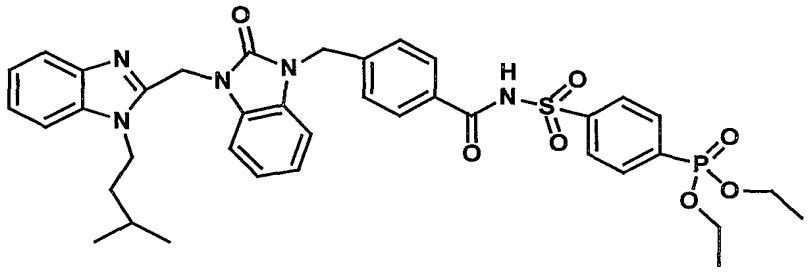
13

A mixture of acid **8** (3.20 g, 6.82 mmol), 2-carbomethoxybenzenesulfonamide (1.76 g, 8.18 mmol), EDC (1.57 g, 8.18 mmol), and DMAP (1.00 g, 8.18 mmol) in CH_2Cl_2 (150 ml) was stirred at ambient temperature for 12 hours. The solution was diluted with CH_2Cl_2 (150 ml), washed with 1N HCl (200 ml) and brine. The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column which was pre-treated with 0.1% acetic acid in CH_2Cl_2 and eluted with EtOAc, and then 5% to10% MeOH in EtOAc to afford 4.13 g (91%) of compound **13** as white solid:

^{1}HNMR (CD_3OD) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.40-1.48 (m, 2 H), 1.60-1.69 (m, 1 H), 3.74 (s, 3 H), 4.34 (t, J = 8.0 Hz, 2 H), 5.19 (s, 2 H), 5.48 (s, 2 H), 7.03-7.04 (m, 3 H), 7.17-7.21 (m, 1 H), 7.27-7.38 (m, 4 H), 7.46-7.58 (m, 4 H), 7.64-7.67 (m, 1 H), 8.00 (d, J = 8.2 Hz, 2 H), 8.12-8.15 (m, 1 H);

IR (KBr, cm^{-1}) 3424, 2955, 1709, 1612, 1590, 1542, 1493, 1435, 1348, 1301, 1258, 750;
MS m/e 666 (MH^+);
Anal. Calcd for $C_{36}H_{35}N_5O_6 \cdot 1.85H_2O$: C, 61.85; H, 5.58; N, 10.02
Found: C, 62.24; H, 5.41; N, 9.57.

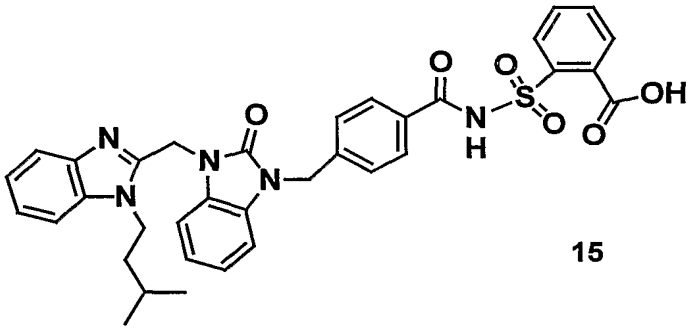
Compound 14



Prepared as described for compound **13**.

^{1}H-NMR (CD_3OD) δ 0.95 (d, J = 6.4 Hz, 6H), 1.35 (t, J = 7.1 Hz, 6H), 1.59-1.72 (m, 3H), 4.12-4.23 (m, 4H), 4.47-4.52 (m, 2H), 5.24 (s, 2H), 5.67 (s, 2H), 7.12-7.14 (m, 3H), 7.24-7.27 (m, 1H), 7.49-7.57 (m, 4H), 7.73 (t, J = 7.1 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.97-8.01 (m, 2H), 8.23 (dd, J = 3.4, 8.4 Hz, 2H);
MS m/e 744 (MH^+);

Compound 15



15

A solution of ester **13** (0.53 g, 0.85 mmol) in THF (1 ml) and MeOH (5 ml) was treated with 1N NaOH (4.23 ml, 4.23 mmol). The solution was stirred at reflux for 12 h. After cooling to room temperature, the solution was acidified with 1N HCl to pH 4.5 and evaporated. The residue was triturated in hot H_2O (10 ml) and filtered. The solid was washed with H_2O and dried in vacuum to give 0.49 g (89% yield) of compound **15** as a white solid:

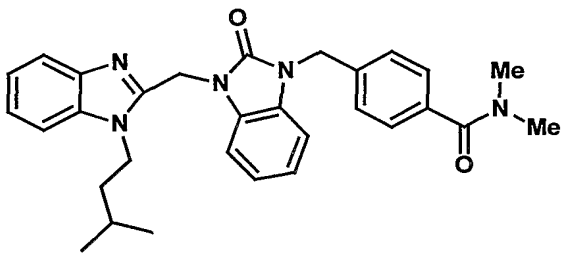
^{1}HNMR (CD_3OD) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.43-1.50 (m, 2 H), 1.60-1.69 (m, 1 H), 4.36 (t, J = 8.1 Hz, 2 H), 5.22 (s, 2 H), 5.51 (s, 2 H), 7.03-7.06 (m, 3 H), 7.20-7.21 (m, 1 H), 7.28-7.37 (m, 2 H), 7.44-7.52 (m, 3 H), 7.60-7.69 (m, 4 H), 7.91 (d, J = 8.3 Hz, 2 H), 8.19-8.21 (d, J = 7.4 Hz, 1 H);
IR (KBr, cm^{-1}): 3424, 2957, 1710, 1612, 1591, 1563, 1528, 1512, 1492, 1439, 1406, 1348, 1173, 750;
MS m/e 652 (MH^+);

Anal. Calcd for $C_{35}H_{33}N_5O_6 \bullet H_2O$ C, 62.77; H, 5.27; N, 10.46
Found: C, 62.61; H, 5.45; N, 10.27.

A suspension of the acid (1.20 g, 1.84 mmol) in MeOH (50 ml) was triturated with 1N NaOH (3.67 ml, 3.67 mmol) to pH 7.8 and filtered. The filtrate was lyophilized to yield 1.20 g (94% yield) of a white solid as a disodium salt of compound **15**:

^{1}HNMR (CD_3OD) δ 0.91 (d, J = 6.6 Hz, 6 H), 1.41-1.49 (m, 2 H), 1.62-1.69 (m, 1 H), 4.36 (t, J = 8.1 Hz, 2 H), 5.20 (s, 2 H), 5.49 (s, 2 H), 7.00-7.04 (m, 3 H), 7.17-7.20 (m, 1 H), 7.25-7.49 (m, 8 H), 7.65-7.68 (m, 1 H), 7.99-8.03 (m, 3 H);
IR (KBr, cm^{-1}) 3424, 2956, 1707, 1608, 1592, 1565, 1504, 1493, 1403, 1330, 1154, 750;
MS m/e 652 (MH^+);
Anal. Calcd for $C_{35}H_{31}N_5Na_2O_6 \bullet 4H_2O$: C, 54.75; H, 5.12; N, 9.12
Found: C, 54.87; H, 5.01; N, 9.11.

Compound 16



Compound **16** was prepared by the same procedure as compound **9** using acid **8** and dimethylamine hydrochloride:

^{1}HNMR (CD_3OD) δ 1.66-1.76 (m, 3H), 2.98 (s, 3H), 3.10 (s, 6H), 4.57 (t, J = 8.3 Hz, 2H), 5.23 (s, 2H), 5.76 (s, 2H), 7.16-7.21 (m, 2H), 7.29-7.31 (m, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.59-7.66 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H);

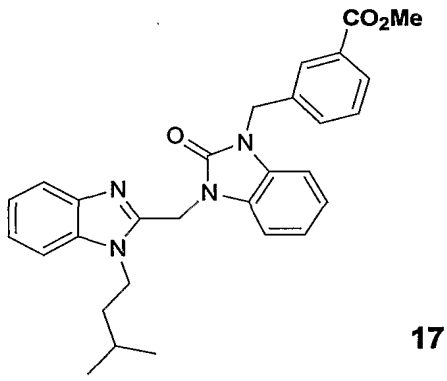
MS m/e 496 (MH^+);

IR (KBr, cm^{-1}) 3424, 1708, 1634, 1494, 1404, 1190, 751

Anal. Calcd for $C_{30}H_{33}N_5O_2 \bullet 1.0TFA \bullet H_2O$: C, 61.24; H, 5.78; N, 11.16

Found: C, 61.10; H, 5.41; N, 10.83

Compound 17



17

Compound **17** was prepared as a white powder in 87% yield using the same procedure as compound **7** with compound **6** and *m*-bromomethylbenzoic acid methyl ester:

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.47 (m, 2H), 1.69 (m, 1H), 3.91 (s, 3H), 4.32 (m, 2H), 5.15 (s, 2H), 5.46 (s, 2H), 6.84 (d, J = 8.9 Hz, 1H), 6.99 (m, 2H), 7.31 (m, 3H), 7.40 (m, 2H), 7.52 (d, J = 7.3 Hz, 1H), 7.81 (m, 1H), 7.97 (d, J = 8.3 Hz, 1H), 8.05 (s, 1H);

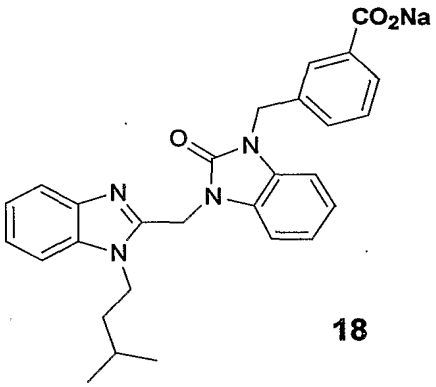
IR (KBr, cm^{-1}) 3405, 2952, 1707, 1497, 1407, 1291, 747.

MS m/e 483 (MH^+);

Anal. Calcd for $C_{29}H_{30}N_4O_3$: C, 72.18; H, 6.27; N, 11.61

Found: C, 72.08; H, 6.32; N, 11.42

Compound 18



18

Compound **18** was prepared as a white powder in 77% yield using the same procedure as for compound **8**:

^{1}H NMR (DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6H), 1.43 (m, 2H), 1.64 (m, 1H), 4.32 (m, 2H), 5.09 (s, 2H), 5.42 (s, 2H), 6.99 (m, 2H), 7.08 (m, 1H), 7.19 (m, 5 H), 7.49 (d, J = 7.3 Hz, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.81 (s, 1H);

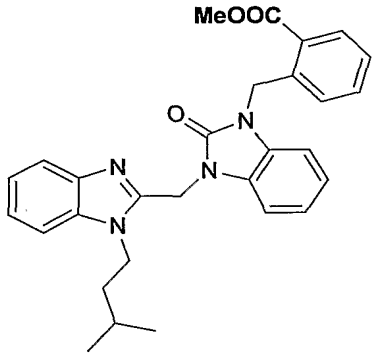
IR (KBr, cm^{-1}) 3401, 2955, 1702, 1565, 1493, 1391, 750;

MS m/e 469 (MH^+);

Anal. Calcd for $C_{28}H_{27}N_4O_3Na \cdot 2.25\ H_2O$: C, 63.32; H, 5.97; N, 10.55

Found: C, 63.31; H, 5.62; N, 10.41

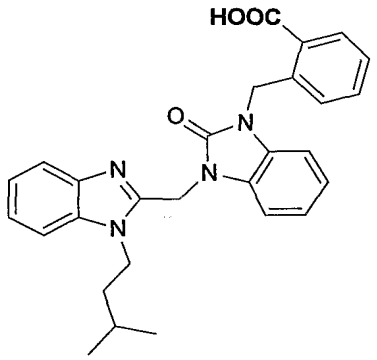
Compound 19



Compound **6** (5.0 g, 14.95 mmol), *o*-bromomethylbenzoic acid methyl ester (4.43g, 19.44 mmol) and Cs_2CO_3 (14.62, 44.85 mmol) were stirred at reflux in acetone (200 mL) for 1 hour. The solvent was evaporated and the residue dissolved in CH_2Cl_2 and filtered. The filtrate was washed with water, dried over $MgSO_4$ and evaporated. The residue was triturated in EtOAc to give 6.37 g (88% yield) of compound **19** as a white solid:

^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 6 H), 1.42-1.50 (m, 2 H), 1.65-1.74 (m, 1 H), 3.96 (s, 1 H), 4.29-4.35 (m, 2 H), 5.46 (s, 2 H), 5.58 (s, 2 H), 6.79 (d, J = 7.9 Hz, 1 H), 6.95-7.06 (m, 3 H), 7.27-7.38 (m, 4 H), 7.48 (d, J = 7.1 Hz, 1 H), 7.78-7.81 (m, 1 H), 8.06 (dd, J = 1.6, 7.6 Hz, 1 H);
IR (KBr, cm^{-1}) 1707, 1497, 1403, 1284, 1257, 739;
MS m/e 483 (MH^+);
Anal. Calcd for $C_{29}H_{30}N_4O_3$: C, 72.18; H, 6.27; N, 11.61
C, 71.96; H, 6.21; N, 11.41.

Compound 20



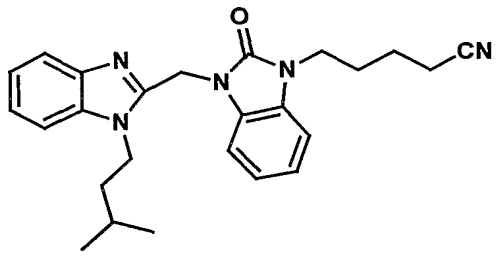
20

Compound **20** was prepared using the same procedure as for compound **8**.

^{1}H NMR (DMSO-d_6) δ 0.91 (d, J = 6.7 Hz, 6 H), 1.40-1.47 (m, 2 H), 1.61-1.70 (m, 1 H), 4.30-4.35 (m, 2 H), 5.43 (s, 2 H), 5.55 (s, 2 H), 6.85 (dd, J = 1.5, 7.9 Hz, 1 H), 6.89-6.98 (m, 2 H), 7.06-7.26 (m, 6 H), 7.50 (d, J = 7.4 Hz, 1 H), 7.61 (d, J = 6.8 Hz, 1 H), 7.69 (dd, J = 1.9, 7.4 Hz, 1 H);
IR (KBr, cm^{-1}) 3403, 2956, 1701, 1609, 1586, 1562, 1493, 1396, 742;
MS m/e 469 (MH^+);

Anal. Calcd for $C_{29}H_{27}NaN_4O_3 \bullet$ 1.85 H_2O: C, 64.19; H, 5.90; N, 10.64
Found: C, 63.78; H, 5.49; N, 10.50.

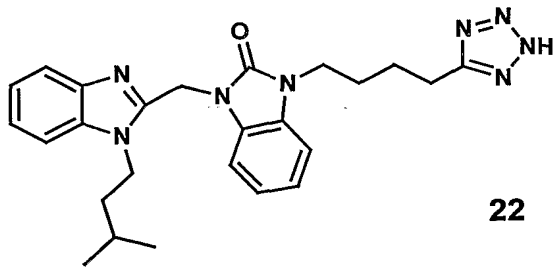
Compound 21



Compound **21** was prepared using the same procedure as for compound **7** with compound **6** and 5-bromovaleronitrile:

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.43 (m, 2H), 1.63-1.81 (m, 3H), 1.97 (m, 2H), 2.46 (t, J = 7.1 Hz, 2H), 3.99 (t, J = 6.8 Hz, 2H), 4.30 (m, 2H), 5.40 (s, 2H), 6.96-7.12 (m, 3H), 7.29 (m, 3H), 7.44 (d, J = 7.2 Hz, 1H), 7.80 (m, 1H);
MS m/e 416 (MH^+).

Compound 22

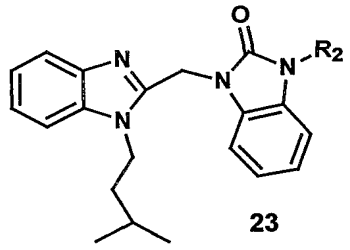


22

Nitrile **21** (2.89g, 6.96 mmol), ammonium chloride (1.12g, 20.87 mmol)

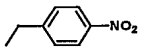
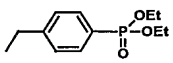
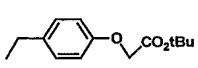
and sodium azide (1.36 g, 20.87 mmol) were mixed in anhydrous DMF (100 mL) and stirred at 110 °C for 1 day. After additional ammonium chloride (1.12g, 20.87 mmol) and sodium azide (1.36 g, 20.87 mmol) were added, the mixture was stirred for additional 2 days at 110 °C. The solvent was evaporated and the residue purified by silica gel column chromatography (gradient, MeOH in EtOAc 0 to 10%). The residue was dissolved in 1 N NaOH and chromatographed on a C18 column using 10 to 40% MeOH/water to give 1.2 g (38% yield) of compound **22**:

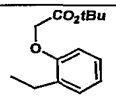
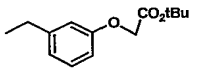
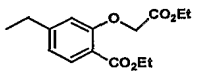
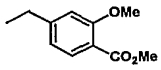
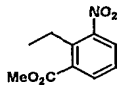
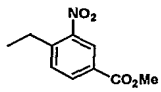
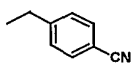
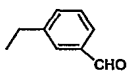
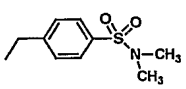
^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.60 (m, 2H), 1.70 (m, 1H), 1.91 (m, 2H), 2.00 (m, 2H), 3.03 (t, J = 7.1 Hz, 2H), 4.00 (t, J = 6.8 Hz, 2H), 4.29 (m, 2H), 5.40 (s, 2H), 6.90 (m, 1H), 7.03 (m, 2H), 7.20-7.36 (m, 4H), 7.60 (d, J = 7.5 Hz, 1H); MS m/e 459 (MH^+).

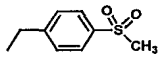
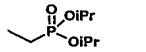
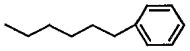
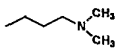
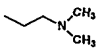
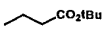
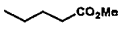
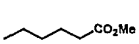


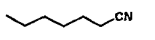
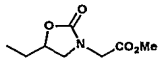
23

Table 2- Compounds listed below were prepared by alkylation of compound **6** as described for the preparation of compound **7**.

#	R_2	^{1}H-NMR Data	MS Data
23a[a]		($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.46-1.54 (m, 2H), 1.67-1.74 (m, 1H), 4.38-4.43 (m, 2H), 5.21 (s, 2H), 5.58 (bs, 2H), 6.82 (d, J = 7.4 Hz, 1H), 7.02-7.14 (m, 2H), 7.38 (bs, 3H), 7.49 (d, J = 8.7 Hz, 2H), 7.64-7.71 (m, 1H), 7.84-7.92 (m, 1H), 8.20 (d, J = 8.8 Hz, 2H)	470 (MH^+)
23b[b]		($CDCl_3$) δ 0.96 (d, J = 6.5 Hz, 6H), 1.32 (t, J = 7.1 Hz, 6H), 1.45-1.74 (m, 3H), 4.03-4.19 (m, 4H), 4.38 (t, J = 7.9 Hz, 2H), 5.16 (s, 2H), 5.54 (s, 2H), 6.84-6.87 (m, 1H), 7.03-7.08 (m, 2H), 7.41-7.45 (m, 5H), 7.53-7.59 (m, 1H), 7.75-7.86 (m, 3H)	561 (MH^+)
23c[c]		(DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6H), 1.40 (s, 9H), 1.39-1.47 (m, 2H), 1.61-1.65 (m, 1H), 4.20-4.33 (m, 2H), 4.59 (s, 2H), 5.03 (s, 2H), 5.40 (s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.97-7.00 (m, 2H), 7.14-7.26 (m, 4H), 7.29 (d, J = 14.7 Hz, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H)	554 (MH^+)
23d[c]		(DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6H), 1.44 (s, 11H), 1.54-1.68 (m, 1H), 4.31-4.38 (m, 2H), 4.81 (s, 2H), 5.16 (s, 2H), 5.43 (s, 2H), 6.82-7.08 (m, 4H),	554 (MH^+)

		7.10-7.12 (m, 2H), 7.15-7.31 (m, 4H), 7.51-7.58 (m, 1H), 7.59-7.64 (m, 1H)	
23e[c]		(DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6H), 1.37 (s, 9H), 1.41-1.48 (m, 2H), 1.59-1.66 (m, 1H), 4.28-4.34 (m, 2H), 4.59 (s, 2H), 5.05 (s, 2H), 5.40 (s, 2H), 6.76-6.80 (dd, J = 2.2, 7.9 Hz, 1H), 6.90-7.01 (m, 4H), 7.09-7.26 (m, 5H), 7.48 (d, J = 7.4 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H)	554 (MH^+)
23f[a]		(DMSO-d_6) δ 0.91(d, J = 5.3 Hz, 6H), 1.17 (d, J = 7.1 Hz, 3H), 1.30 (d, J = 7.1 Hz, 3H), 1.48-1.60 (m, 2H), 1.61-1.75 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 6.9 Hz, 2H), 4.43 (t, J = 7.8 Hz, 2H), 4.82 (s, 2H), 5.12 (s, 2H), 5.58 (s, 2H), 7.00-7.01 (m, 2H), 7.10-7.23 (m, 2H), 7.30-7.43 (m, 5H), 7.60 (d, J = 7.5 Hz, 1H), 7.68-7.73 (m, 2H)	641 (MH^+)
23g[a]		(DMSO-d_6) δ 0.90 (d, J = 6.5 Hz, 6H), 1.41-1.55 (m, 2H), 1.49-1.67 (m, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 4.82 (t, J = 7.6 Hz, 2H), 5.16 (s, 2H), 5.43 (s, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.99-7.04 (m, 2H), 7.15-7.26 (m, 5H), 7.53 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.9 Hz, 2H)	512 (MH^+)
23h[a]		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.38-1.45 (m, 2H), 1.56-1.64 (m, 1H), 3.64 (s, 3H), 4,24 (t, J = 7.8 Hz, 2H), 5.30 (s, 2H), 5.49 (s, 2H), 6.88-6.91 (m, 1H), 6.91-7.02 (m, 2H), 7.15-7.27 (m, 3H), 7.50 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.99 (d, J = 6.9 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H)	527 (MH^+)
23i[a]		(DMSO-d_6) δ 0.93 (d, J = 6.3 Hz, 6H), 1.42-1.58 (m, 2H), 1.60-1.78 (m, 1H), 3.91 (s, 3H), 4.36 (t, J = 7.5 Hz, 2H), 5.48 (s, 2H), 5.59 (s, 2H), 6.99-7.10 (m, 2H), 7.12-7.30 (m, 4H), 7.35 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 8.18 (dd, J = 1.5, 7.9 Hz, 1H), 8.63 (d, J = 1.5 Hz, 1H)	527 (MH^+)
23j[a]		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.40-1.50 (m, 2H), 1.58-1.65 (m, 1H), 4.31 (t, J = 7.8 Hz, 2H), 5.22 (s, 2H), 5.43 (s, 2H), 6.95-7.10 (m, 2H), 7.10-7.18 (m, 4H), 7.42-7.56 (m, 3H), 7.60 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H)	449 (MH^+)
23k[d]		($CDCl_3$) δ 0.95 (d, J = 6.5 Hz, 6H), 1.42-1.51 (m, 2H), 1.63-1.78 (m, 1H), 4.41 (t, J = 8.4 Hz, 2H), 5.18 (s, 2H), 5.59 (s, 2H), 6.88-6.89 (m, 1H), 7.02-7.08 (m, 2H), 7.36-7.38 (m, 3H), 7.51-7.62 (m, 3 H), 7.80-7.87 (m, 3H), 10.0 (s, 1H)	453 (MH^+)
23l[d]		(CD_3OD) δ 0.95 (d, J = 6.5 Hz, 6 H), 1.61-1.66 (m, 3 H), 2.65 (s, 6 H), 4.50-4.53 (m, 2 H), 5.27 (s, 2 H), 5.70 (s, 2 H), 7.14-7.17 (m, 3 H), 7.25-7.28 (m, 1 H), 7.53-7.64 (m, 4 H), 7.71-7.79 (m, 4	532 (MH^+)

		H)	
23m[d]		(CD_3OD) δ 0.95 (d, J = 6.5 Hz, 6 H), 1.61-1.66 (m, 3 H), 2.65 (s, 6 H), 4.50-4.53 (m, 2 H), 5.27 (s, 2 H), 5.70 (s, 2 H), 7.14-7.17 (m, 3 H), 7.25-7.28 (m, 1 H), 7.53-7.64 (m, 4 H), 7.71-7.79 (m, 4 H)	503 (MH^+)
23n[c]		(DMSO-d_6) δ 0.93 (d, J = 5.5 Hz, 6H), 1.15 (d, J = 6.2 Hz, 6H), 1.19 (d, J = 6.2 Hz, 6H), 1.46-1.53 (m, 2H), 1.61-1.67 (m, 1H), 4.29-4.34 (s, 2H), 4.35 (s, 2H), 4.52 -4.62 (m, 2H), 5.37 (s, 2H), 6.98-7.07 (m, 2H), 7.09-7.26 (m, 4H), 7.48-7.56 (m, 2H)	512 (MH^+)
23o[c]		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.22-1.42 (m, 4H), 1.58-1.74 (m, 3H), 1.91-2.01 (m, 2H), 3.88 (t, J = 6.9 Hz, 2H), 4.29 (t, J = 8.1 Hz, 2H), 4.58 (t, J = 8.1 Hz, 2H), 5.35 (s, 2H), 6.98-7.07 (m, 2H), 7.14-7.30 (m, 4H), 7.49 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 8.12 (t, J = 7.1 Hz, 2H), 8.56 (t, J = 7.9 Hz, 1H), 9.04 (d, J = 5.5 Hz, 2H)	482 (MH^+)
23p[c]		($CDCl_3$) δ 0.85 (d, J = 6.6 Hz, 6H), 1.06 (t, J = 7.4 Hz, 3H), 1.34-1.41 (m, 2H), 1.61-1.86 (m, 3H), 3.87 (t, J = 7.3 Hz, 2H), 4.25-4.31 (m, 2H), 5.53 (s, 2H), 6.95-7.08 (m, 3H), 7.23-7.31 (m, 3H), 7.40 (dd, J = 0.6, 1.6 Hz, 1H), 7.77-7.80 (m, 1H)	377 (MH^+)
23q[e]		($CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 6H), 1.36-1.43 (m, 2H), 1.60-1.73 (m, 1H), 2.08-2.20 (m, 2H), 2.40 (s, 6H), 2.54 (t, J = 6.9 Hz, 2H), 4.00 (t, J = 6.9 Hz, 2H), 4.26 (t, J = 6.9 Hz, 2H), 5.38 (s, 2H), 6.90-7.10 (m, 3H), 7.22-7.31 (m, 3H), 7.37-7.40 (m, 1H), 7.74-7.80 (m, 1H)	420 (MH^+)
23r[b]		($CDCl_3$)δ 0.95 (d, J = 6.6 Hz, 6H), 1.35-1.43 (m, 2H), 1.64-1.75 (m, 1H), 2.36 (s, 6H), 2.67 (t, J = 7.2 Hz, 2H), 4.05 (t, J = 7.2 Hz, 2H), 4.27-4.32 (m, 2H), 5.42 (s, 2H), 7.00-7.11 (m, 3H), 7.28-7.34 (m, 3H), 7.40-7.43 (m, 1H), 7.79-7.83 (m, 1H)	406 (MH^+)
23s[b]		($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 6H), 1.41 (s, 9H), 1.65-1.74 (m, 1H), 2.72 (t, J = 7.5 Hz, 2H), 4.18 (t, J = 7.4 Hz, 2H), 4.27-4.33 (m, 2H), 5.40 (s, 2H), 6.99-7.09 (m, 3H), 7.25-7.31 (m, 3H), 7.43 (d, J = 7.4 Hz, 1H), 7.78-7.81 (m, 1H)	463 (MH^+)
23t[b]		($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.36-1.44 (m, 2H), 1.65-1.74 (m, 1H), 2.06-2.15 (m, 2H), 2.43 (t, J = 7.2 Hz, 2H), 3.98 (t, J = 7.2 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.28-4.33 (m, 2H), 5.42 (s, 2H), 7.00-7.11 (m, 3H), 7.28-7.34 (m, 3H), 7.44 (d, J = 7.2 Hz, 1H), 7.79-7.82 (m, 1H)	449 (MH^+)
23u[b]		(CD_3OD) δ 1.66-1.72 (m, 2H), 1.83-1.88 (m, 2H), 2.41 (t, J = 7.2 Hz, 2H), 3.14 (s, 6H), 3.62 (s, 3H), 3.87 (t, J = 8.0 Hz, 2H), 4.02 (t, J = 6.8 Hz, 2H),	450 (MH^+)

		5.19 (t, J = 7.8 Hz, 2H), 5.86 (s, 2H), 7.22-7.34 (m, 3H), 7.45-7.48 (m, 1H), 7.67-7.79 (m, 3H), 8.11 (d, J = 8.0 Hz, 1H)	
23v[b]		($CDCl_3$) δ 0.95 (d, J = 6.56 Hz, 6H), 1.26-1.88 (m, 9H), 2.36 (t, J = 6.99, 2H), 3.94 (t, d = 7.05 Hz, 2H), 4.29 (m, 2H), 5.41 (s, 2H), 6.95-7.81 (m, 8H)	430 (MH^+)
23w[b]		(CD_3OD) δ 0.97 (dd, J = 2.8, 6.6 Hz, 6H), 1.36-1.64 (m, 2H), 1.68-1.78 (m, 1H), 3.67-3.72 (m, 1H), 3.70 (s, 3H), 3.84-3.87 (m, 1H), 4.02 (dd, J = 14.1, 18.0 Hz, 2H), 4.28-4.87 (m, 2H), 5.01-5.12 (m, 1H), 5.47 (dd, J = 16.3, 22.1 Hz, 2H), 7.05-7.17 (m, 3H), 7.28-7.33 (m, 3H), 7.49 (d, J = 7.3 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H)	506 (MH^+)

a, Cs_2CO_3 used as base; **b**, BEMP used as base; **c**, BTPP used as base; **d**, prepared as described in J. Am. Chem. Soc. 1991, 4208; **e**, NaH used as base.

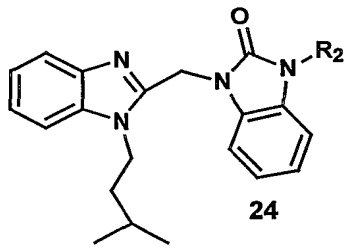


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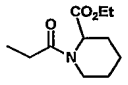
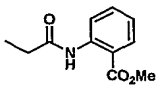
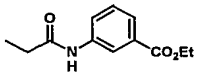
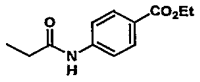
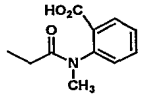
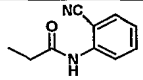
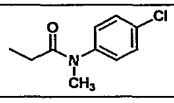
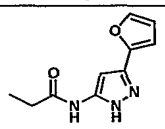
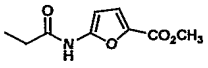
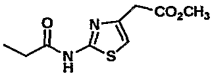
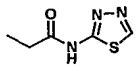
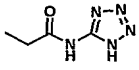
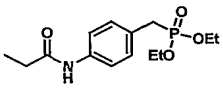
Table 3- Compounds were prepared by convering the acetic acid or benzoic acid to an acid chloride with $SOCl_2$ or oxalyl chloride and treating the acid chloride with corresponding amine unless otherwise noted.

#	R_2	^{1}H-NMR Data	MS Data
24a		(DMSO-d_6) δ 0.92 (d, J = 6.5 Hz, 6H), 1.15-1.28 (m, 5H), 1.38-1.60 (m, 2H), 1.60-1.75 (m, 3H), 1.99-2.20 (m, 1H), 2.20-2.30 (m, 1H), 3.98-4.04 (m, 1H), 4.11 (q, J = 7.0 Hz, 2H), 4.18-4.31 (m, 3H), 4.62-4.84 (m, 1H), 4.91-5.00 (m, 2H), 5.37 (s, 2H), 6.95-7.10 (m, 3H), 7.15-7.26 (m, 3H), 7.50 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.4 Hz, 1H)	531 (MH^+)
24b		(DMSO-d_6) δ 0.90 (dd, J = 2.8, 6.5 Hz, 6H), 1.35-1.45 (m, 2H), 1.47-1.71 (m, 1H), 3.17 (s, 3H), 4.00-4.21 (m, 1H), 4.32 (t, J = 7.2 Hz, 2H), 4.71 (s, 1H), 4.86 (s, 1 H), 5.40 (d, J = 4.9 Hz, 2H), 6.92 (t, J = 7.0 Hz, 1H), 6.99-7.07 (m, 2H), 7.16-7.34 (m, 3H), 7.50 (d, J = 7.9 Hz, 1H), 7.59-7.65 (m, 1H), 7.88 (d, J = 6.5 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 7.4 Hz, 1H)	525 (MH^+)
24c		(DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.35-1.55 (m, 2H), 1.61-1.75 (m, 1H), 4.26-4.33 (m, 4H), 4.79 (m, 2H), 5.39 (m, 2H), 7.02-7.06 (m, 2H), 7.16-7.28 (m, 5H), 7.40-7.55 (m, 2H), 7.56-7.72 (m, 2H), 7.80-7.81 (m, 1H), 8.26 (s, 1H)	539 (MH^+)
		(DMSO-d_6) δ 0.90 (d, J = 6.6 Hz, 6H),	540 (MH^+)

24d		1.30 (t, J = 7.1 Hz, 3H), 1.40-1.44 (m, 2H), 1.51-1.67 (m, 1H), 4.24-4.34 (m, 3H), 4.81 (s, 2H), 5.40 (s, 2H), 7.03-7.05 (m, 2H), 7.08-7.26 (m, 4H), 7.50 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.92 (d, J = 8.7 Hz, 2H)	
24e		($CDCl_3$) δ 0.94 (d, J = 6.54 Hz, 6H), 1.48 (m, 1H), 1.66 (m, 1H), 3.17 (s, 3H), 4.03 (m, 1H), 4.42 (m, 3H), 5.34 (m, 2H), 6.55 (m, 1H), 6.69 (d, J = 7.68 Hz, 1H), 7.11 (m, 1H), 7.34 (m, 5H), 7.55 (t, J = 7.65 Hz, 1H), 7.66 (t, J = 7.56 Hz, 1H), 7.88 (d, J = 9.06 Hz, 1H), 8.29 (d, J = 7.65 Hz, 1H)	526 (MH^+)
24f		($CDCl_3$) δ 0.95 (d, J = 8.78 Hz, 6H), 1.48 (m, 2H), 1.64 (m, 1H), 4.32 (m, 2H), 4.76 (s, 2H), 5.44 (s, 2H), 7.07 - 7.76 (m, 11H), 8.24 (d, J = Hz, 1H), 8.66 (s, 1H)	493 (MH^+)
24g		($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 6H, 1.52 - 1.69 (m, 3H), 3.28 (s, 3H), 4.37 (m, 4H), 5.52 (s, 2H), 6.83-7.89 (m, 12H)	516 (MH^+)
24h		($CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 6H), 1.37 (m, 2H), 1.56 (m, 1H), 4.18 (m, 2H), 4.61 (s, 1H), 5.33 (s, 1H), 6.29 (m, 1H), 6.46 (m, 1H), 6.58 (m, 1H), 6.89 - 7.33 (m, 8H), 7.65 (m, 1H)	524 (MH^+)
24i		($CDCl_3$) δ 0.97 (d, J = 6.57 Hz, 6H), 1.29-1.69 (m, 3H), 3.84 (s, 3H), 4.32 (m, 2H), 4.72 (s, 1H), 5.46 (s, 1H), 6.55 (d, J = 3.66 Hz, 1H), 6.91-7.43 (m, 8H, 7.77 (m, 1H)	516 (MH^+)
24j		($CDCl_3$) δ 0.96 (d, J = 6.51 Hz, 6H), 1.25 (t, J = 7.14 Hz, 3H), 1.38 (m, 2H), 1.55 (m, 1H), 3.65 (s, 2H), 4.06 (q, J = 7.14 Hz, 2H), 4.30 (m, 2H), 4.81 (s, 2H), 5.42 (s, 2H), 6.80 (s, 1H), 7.00 - 7.61 (m, 4H), 7.74 (m, 1H)	561 (MH^+)
24k		($CDCl_3$) δ 0.99 (d, J = 6.6 Hz, 6H), 1.57 (m, 2H), 1.74 (m, 1H), 4.35 (m, 2H), 5.08 (s, 2H), 5.52 (s, 2H), 7.00 - 7.45 (m, 7H), 7.82 (m, 1H), 8.82 (s, 1H)	476 (MH^+)
24l[a]		(DMSO-d_6) δ 0.90-0.98 (m, 6H), 1.15-1.23 (m, 2H), 1.60-1.72 (m, 1H), 4.28-4.35 (m, 2H), 5.38 (s, 2H), 6.95-7.03 (m, 3H), 7.15-7.29 (m, 3H), 7.47-7.51 (m, 1H), 7.51-7.63 (m, 1 H)	459 (MH^+)
24m		($CDCl_3$) δ 0.96 (d, J = 6.57 Hz, 6H), 1.25 (t, J = 7.05 Hz, 6H), 1.56 (m, 1H), 1.72 (m, 1H), 3.10 (d, J = 21.45 Hz, 2H), 3.99 (m, 4H), 4.29 (m, 2H), 4.59 (s, 2H), 5.40 (s, 2H), 7.05-7.37 (m , 9H), 7.46 (d, J = 8.19 Hz, 2H), 7.73 (m, 1H), 8.83 (s, 1H)	618 (MH^+)

a, prepared using EDC as coupling reagent.

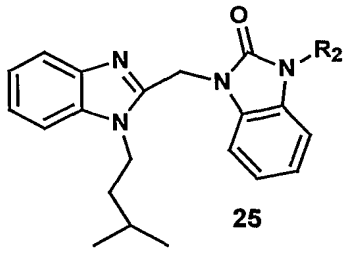


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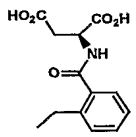
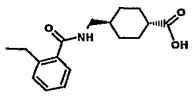
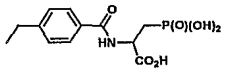
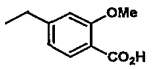
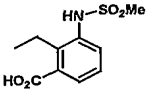
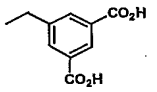
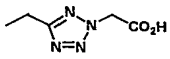
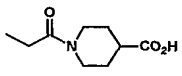
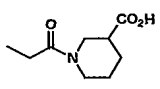
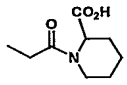
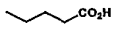
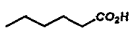
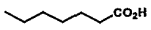
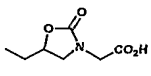
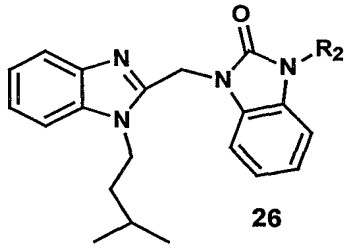
Table 4- Acids were prepared by hydrolysis of the corresponding ester using NaOH/MeOH as previously described for compound **8**.

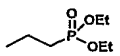
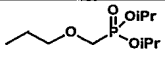
#	R_2	^{1}H-NMR Data	MS Data
25a		(DMSO-d_6) δ 0.87 (d, J = 6.5 Hz, 6H), 1.38-1.52 (m, 2H), 1.58-1.63 (m, 1H), 3.38-3.48 (m, 1H), 4.24-4.33 (m, 2H), 4.38 (s, 2H), 5.29 (s, 2H), 5.41 (d, J = 4.3 Hz, 2H), 6.89-7.00 (m, 2H), 7.06-7.10 (m, 2H), 7.12-7.24 (m, 5H), 7.46-7.58 (m, 3 H)	629 (MH^+)
25b		(DMSO-d_6) δ 0.90 (d, J = 6.5 Hz, 6H), 0.97-1.06 (m, 2H), 1.14-1.29 (m, 2H), 1.46-1.53 (m, 3H), 1.62-1.69 (m, 1H), 1.80-1.98 (m, 4H), 2.09-2.17 (m, 1H), 3.13 (t, J = 6.2 Hz, 2H), 4.40 (t, J = 8.0 Hz, 2H), 5.22 (s, 2H), 5.56 (s, 2H), 7.00-7.09 (m, 4H), 7.28-7.38 (m, 5H), 7.46-7.49 (m, 1H), 7.68 (d, J = 7.8 Hz, 2H), 8.58 (t, J = 5.7 Hz, 1H)	608 (MH^+)
25c		(CD_3OD) δ 0.90 (d, J = 6.6 Hz), 1.36-1.43 (m, 2 H), 1.59-1.69 (m, 1 H), 1.99-2.18 (m, 2 H), 4.30-4.37 (m, 2), 4.46-4.57 (m, 1 H), 5.22 (s, 2 H), 5.49 (s, 2 H), 6.98-7.09 (m, 3 H), 7.15-7.19 (m, 1 H), 7.25-7.38 (m, 2 H), 7.42-7.51 (m, 3 H), 7.64-7.69 (m, 1 H), 7.89 (d, J = 8.4 Hz, 2 H)	664 (MH^+)
25d		(DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6H), 1.40-1.45 (m, 2H), 1.58-1.65 (m, 1H), 3.79 (s, 3H), 4.25-4.38 (m, 2H), 5.16 (s, 2H), 5.44 (s, 2H), 6.87 (d, J = 8.1 Hz, 1H), 7.02-7.12 (m, 2H), 7.16-7.30 (m, 4H), 7.52 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H)	498 (MH^+)
25e		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.35-1.42 (m, 2H), 1.58-1.60 (m, 1H), 2.98 (s, 3H), 4.25-4.39 (m, 2H),5.38 (s, 2H), 5.42 (s, 1H), 5.81 (s, 2H), 6.95 -7.12 (m, 2H), 7.12-7.32 (m, 3H), 7.35-7.73 (m, 3H)	561 (MH+)
25f		(CD_3OD) δ 0.91 (d, J = 6.6 Hz, 6H), 1.40-1.47 (m, 2H), 1.59-1.65 (m, 1H), 4.37 (t, J = 8.0 Hz, 2H), 5.27 (s, 2H), 5.52 (s, 2H), 7.01-7.14 (m, 3H), 7.18-7.20 (m, 1H), 7.28-7.33 (m, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.66-7.69 (m, 1H), 8.12 (s, 2H), 8.56 (d, J = 1.4 Hz, 1H)	513 (MH^+)
25g		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.32-1.48 (m, 2H), 1.51-1.71 (m, 1H), 4.27-4.35 (m, 2H), 4.78-4.85 (s, 2H), 5.27-5.45 (s, 2H), 6.92-7.05 (m, 2H), 7.10-7.28 (m, 4H), 7.50 (d, J = 7.9 Hz, 1H), 7.58-7.62 (m, 1H)	474 (MH^+)
25h		(DMSO-d_6) δ 0.92 (d, J = 6.6 Hz, 6H), 1.35-1.51 (m, 4 H), 1.52-1.68 (m, 2H), 1.69-1.82 (m, 2H), 1.92-2.10 (m, 1H), 2.62-2.82 (m, 1H), 3.08-3.18 (m, 1H), 3.71-3.88 (m, 1H), 3.90-4.02 (m, 1H), 4.29-4.36 (m, 2H), 4.77-4.85 (m, 1H), 5.36 (s, 2H), 7.01-7.16 (m, 3H), 7.18-7.28 (m, 3H), 7.49 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H)	503 (MH^+)
25i		(DMSO-d_6) δ 0.89-0.93 (m, 6H), 1.34-1.48 (m, 4H), 1.58-1.68 (m, 2H), 1.72-1.93 (m, 1H), 1.95-2.10 (m, 1H), 3.10-3.25 (m, 1H), 3.25-3.50 (m, 2H), 3.70-3.82 (m, 1H), 4.20-4.35 (m, 2H), 4.61-4.79 (m, 2H), 5.20-5.42 (m, 2H), 6.82-7.01 (m, 3H), 7.15-.26 (m, 3H), 7.48 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H)	503 (MH^+)

25j		(DMSO-d_6) δ 0.90-0.93 (m, 6H), 1.23.1.65 (m, 8H), 2.27-2.32 (m, 1H), 2.51-2.71 (m, 1H), 4.02-4.15 (m, 2H), 4.28-4.38 (m, 2H), 4.50-4.59 (m, 1H), 4.76-4.83 (m, 1H), 5.36 (s, 2H), 6.96-6.99 (m, 2H), 7.08-7.26 (m, 3H), 7.49 (d, J = 7.4 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H)	503 (MH^+)
25k		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.30-1.37 (m, 2H), 1.58-1.64 (m, 1H), 1.76-1.83 (m, 2H), 1.91 (t, J = 6.9 Hz, 2H), 3.85 (t, J = 7.2 Hz, 2H), 4.29 (t, J = 8.0 Hz, 2H), 5.36 (s, 2H), 6.95-7.06 (m, 2H), 7.15-7.26 (m, 3H), 7.34 (d, J = 7.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H)	421 (MH^+)
25l		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.32-1.42 (m, 2H), 1.44-1.52 (m, 2H), 1.59-1.67 (m, 3H), 1.97 (t, J = 6.9 Hz, 2H), 3.35 (t, J = 6.2 Hz, 2H), 3.85 (t, J = 6.9 Hz, 2H), 4.26-4.32 (m, 2H), 5.36 (s, 2H), 6.96-7.07 (m, 2H), 7.15-7.26 (m, 4H), 7.48 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H)	435 (MH^+)
25m		(CD_3OD) δ 0.94 (d, J = 6.6 Hz, 6H), 1.31-1.51 (m, 4H), 1.64-1.74 (m, 3H), 1.78-1.88 (m, 2H), 2.19 (t, J = 7.6 Hz, 2H), 3.98 (t, J = 7.3 Hz, 2H), 4.34 (t, J = 8.2 Hz, 2H), 5.45 (s, 2H), 7.01-7.06 (m, 1H), 7.10-7.35 (m, 5H), 7.47 (dd, J = 1.7, 6.9 Hz, 1H), 7.67 (dd, J = 1.7, 6.8 Hz, 1H)	449 (MH^+)
25n		(CD_3OD) δ 0.94 (d, J = 6.3 Hz, 6H), 1.39-1.48 (m, 2H), 1.62-1.70 (m, 1H), 3.58-3.63 (m, 1H), 3.76 (s, 2H), 3.88 (t, J = 9.3 Hz, 1H), 4.19-4.23 (m, 1H), 4.29-4.41 (m, 2H), 4.91-5.02 (m, 2H), 5.44 (s, 2H), 7.03-7.16 (m, 3H), 7.26-7.33 (m, 2H), 7.37 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H)	492 (MH^+)



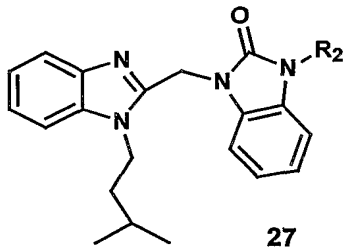
26

Table 5- Phosponates.

#	R_2	^{1}H-NMR Data	MS Data
26a[a]		(DMSO-d_6) δ 0.92 (d, J = 6.6 Hz, 6H), 1.15 (t, J = 7.0 Hz, 6H), 1.38-1.46 (m, 2H), 1.63-1.68 (m, 1H), 2.17-2.28 (m, 2H), 3.90-3.98 (m, 4H), 4.00-4.11 (m, 2H), 4.28-4.34 (m, 2H), 5.35 (s, 2H), 6.98-7.09 (m, 2H), 7.15-7.24 (m, 4H), 7.50 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H)	498 (MH^+)
26b[b]		($CDCl_3$) δ 0.96 (d, J = 6.7 Hz, 6H), 1.21 (d, J = 6.2 Hz, 6H), 1.27 (d, J = 6.2 Hz, 6H), 1.31-1.46 (m, 2H), 1.66-1.75 (m, 1H), 3.74 (d, J = 8.4 Hz, 2H), 3.92 (t, J = 5.4 Hz, 2H), 4.14 (t, J = 5.4	557 (MH^+)

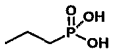
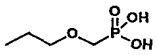
		Hz, 2H), 4.33 (t, J = 8.2 Hz, 2H), 4.60-4.71 (m, 2H), 5.43 (s, 2H), 7.02-7.16 (m, 3H), 7.29-7.32 (m, 3H), 7.44 (d, J = 7.3 Hz, 1H), 7.80-7.84 (m, 1H)	

a, prepared by 1,4-addition to diethylvinyl phosphonate; **b**, alklyation using methanesulfonic acid 2-(diisopropoxy-phosphorylmethoxy)-ethyl ester.

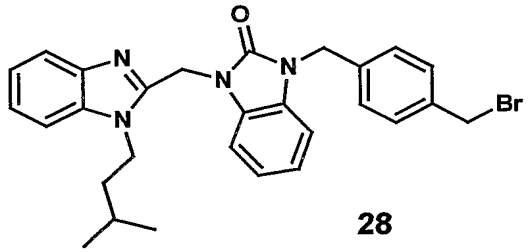


27

Table 5- Phosphonate esters were cleaved with TMSBr.

#	R_2	^{1}H-NMR Data	MS Data
27a		($CDCl_3$) δ 0.80 (d, J = 6.6 Hz, 6H), 1.12-1.22 (m, 2H), 1.47-1.53 (m, 2H), 1.54-1.70 (m, 2H), 3.90-4.05 (m, 2H), 4.19-4.24 (m, 2H), 5.31 (s, 2H), 6.95 (t, J = 8.5 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 7.12-7.31 (m, 4H), 7.43 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 1H)	442 (MH^+)
27b		(CD_3OD) δ 0.95 (d, J = 6.7 Hz, 6H), 1.36-1.44 (m, 2H), 1.62-1.74 (m, 1H), 3.56 (d, J = 8.9 Hz, 2H), 3.88 (t, J = 5.3 Hz, 2H), 4.23 (t, J = 5.4 Hz, 2H), 4.35 (t, J = 8.1 Hz, 2H), 5.47 (s, 2H), 6.97-7.05 (m, 1H), 7.08-7.17 (m, 2H), 7.23-7.34 (m, 3H), 7.47 (d, J = 7.3 Hz, 1H), 7.63-7.68 (m, 1H)	473 (MH^+)

Compound 28



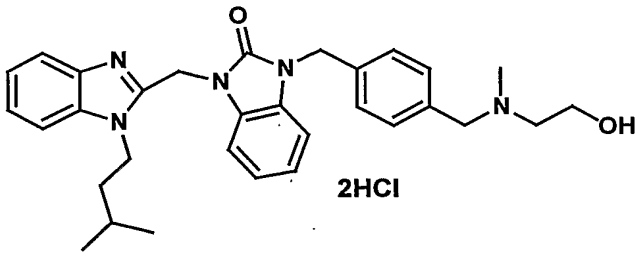
28

Compound **6** (4.01 g, 12 mmol) in CH_2Cl_2 (60 mL) was slowly added to a suspension of α,α'-dibromo-p-xylene (15.84, 60 mmol) and BTPP (9.9 g, 18 mmol) in a mixture of methylene chloride and THF (120 mL, 1:1). The resulting mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc: hexane = 1: 4 to 2:1) to give a product which was triturated in EtOAc/Et_2O to provide 4.12 g (66% yield) of the compound **28** as a white solid:

^{1}H NMR (DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6H), 1.41-1.49 (m, 2H), 1.60-1.67 (m, 1H), 4.32 (t, J = 7.5 Hz, 2H), 4.68 (s, 2H), 5.12 (s, 2H), 5.43 (s, 2H), 7.00-7.04 (m, 2H), 7.15-7.22 (m, 4H), 7.35 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H);
MS m/e 519, 517 (MH^+);

Anal. Calcd for $C_{28}H_{29}BrN_4O$:		C, 64.99; H, 5.65; N, 10.83
	Found:	C, 64.97; H, 5.50; N, 10.57

Compound 29



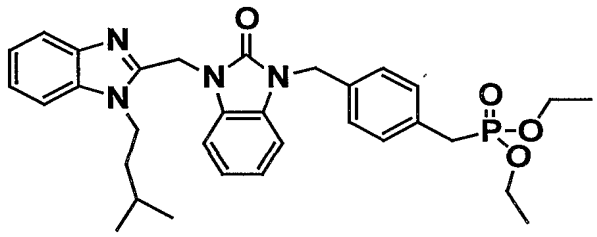
2HCl

Bromide **28** (103 mg, 0.2 mmol) and N-methylaminoethanol (75 mg, 1 mmol) were stirred in methanol (3 mL) overnight. The solvent was evaporated. The residue was diluted with EtOAc, washed with water, dried over $MgSO_4$, and evaporated. To the resulting residue in methanol (2 mL) was added 1N HCl in ether (2 mL). The

solvent was evaporated and the residue was dried in vaccum. The solid was triturated in Et_2O to give 99 mg (80% yield) of compound **29** as white powder:

^1H NMR (DMSO-d_6) δ 0.90 (d, J = 6.5 Hz, 6 H), 1.22-1.38 (m, 2 H), 1.49-1.71 (m, 1 H), 2.66 (d, J = 4.8 Hz, 2 H), 2.97-3.08 (m, 2 H), 3.74 (t, J = 5.6 Hz, 2 H), 4.24 (dd, J = 5.4, 13.0 Hz, 1 H), 4.34 (dd, J = 5.1, 13.0 Hz, 1 H), 4.46 (bt, J = 7.8 Hz, 2 H), 5.15 (s, 2 H), 5.66 (s, 2 H), 7.03-7.09 (m, 2 H), 7.16-7.21 (m, 1 H), 7.35-7.52 (m, 5 H), 7.57 (d, J = 8.1 Hz, 2 H), 7.74 (d, J = 7.2 Hz, 1 H), 7.81 (d, J = 7.7 Hz, 1 H);
IR (KBr, cm^{-1}) 3307, 2955, 2594, 1706, 1613, 1492, 1461, 1405, 750;
MS m/e 512 (MH^+);

Anal. Calcd for $C_{32}H_{40}N_5O_2 \bullet 2HCl \bullet H_2O$ C, 62.23; H, 7.18; N, 11.34
Found: C, 61.96; H, 6.91; N, 11.48.

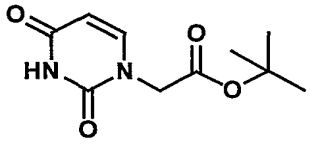


30

A mixture of bromide **28** (160 mg, 0.31 mmol) and triethyl phosphite (536 mg, 3.88 mmol) were stirred at 135 °C for 30 minutes. The mixture was cooled to room temperature, diluted with Et_2O, washed with water, dried over $MgSO_4$, and evaporated. The product was initially an oil that slowly crystallized on standing. The solid was filtered and rinsed with Et_2O to give 160 mg (90% yield) of compound **30**:

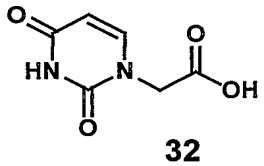
^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.21 (t, J = 7.2 Hz, 6H), 1.41-1.49 (m, 2H), 1.66-1.75 (m, 1H), 3.11 (d, J = 21.3 Hz, 2H), 3.93-4.04 (m, 4H), 4.33 (t, J = 8.1 Hz, 2H), 5.08 (s, 2H), 5.45 (s, 2H), 6.82 (dd, J = 2.1, 6.6 Hz, 1H), 6.94-7.03 (m, 2H), 7.29-7.33 (m, 2H), 7.43-7.46 (m, 1H), 7.79-7.82 (m, 1H)
MS m/e 575 (MH^+).

Compound 31



Uracil (5.0 g, 44.6 mmol) and potassium carbonate (7.4 g, 53.5 mmol) were suspended in DMF. *t*-butyl bromoacetate (9.1 g, 46.8 mmol) was added and the reaction mixture was stirred at 40-50 °C for 18 hours. The solvent was evaporated. The white residue was taken up in water and extracted with EtOAc and $CHCl_3$. The organic extracts were dried over $MgSO_4$ and evaporated. Column chromatography (gradient 2:1 EtOAc/hexanes to 10:1 EtOAc/MeOH) of the residue gave 8.1g (80% yield) of compound **31** as a white solid:

^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9 H), 4.37 (s, 2 H), 5.75 (dd, J = 7.9, 2.0 Hz, 1 H), 7.11 (d, J = 7.9 Hz, 1 H), 9.22 (s, 1 H);
IR (KBr, cm^{-1}) 3051, 1745, 1715, 1681, 1460, 1234, 1151;
MS m/e 325 (MH^+).
Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38
Found: C, 53.09; H, 6.26; N, 12.43.

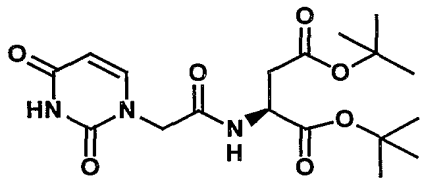


32

To ester **31** (30g, 132.6 mmol) in THF (20 ml) was added 4 N HCl in dioxane (250 mL). The resulting slurry was stirred for 1 day. The solvent was evaporated and the residue was triturated in Et_2O to give 21.81 g (97% yield) of compound **32** as a white solid:

^{1}H NMR (DMSO-d_6) δ 4.41 (s, 2 H), 5.59 (d, J = 7.8 Hz, 1 H), 7.61 (d, J = 7.8 Hz, 1 H);
MS m/e 171 (MH^+).

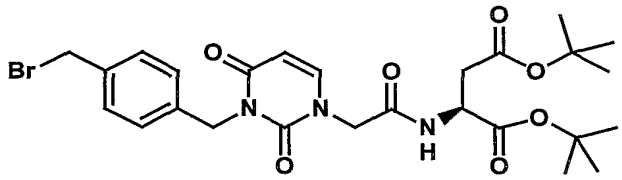
Compound 33



Compound **33** was prepared using the same procedure as for compound **16** with **32** and di-t-butyl aspartate:

^{1}H NMR ($CDCl_3$) δ 1.26 (s, 18H), 2.53 (dd, J = 4.2, 17.4 Hz, 1H), 2.71 (dd, J = 4.8, 17.4 Hz, 1H), 4.20 (d, J = 15.9 Hz, 1H), 4.32 (d, J = 15.9 Hz, 1H), 4.48-4.50 (m, 1H), 5.55 (dd, J = 1.5, 8.1 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 8.70 (bs, 1H);
MS m/e 398 (MH^+).

Compound 34

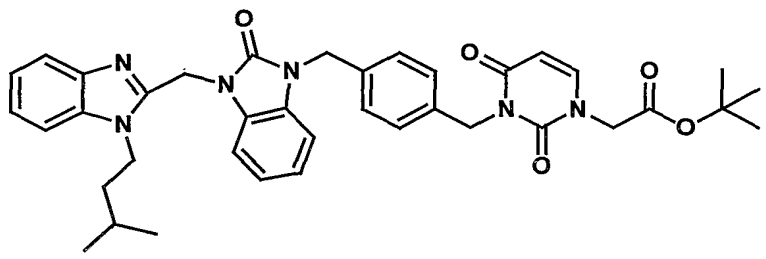


34

A mixture of **33** (39.0 g, 98.1 mmol), α, α'-dibromo-*p*-xylene (77.8 g, 294 mmol) and BTPP (36.8 g, 118 mmol) in THF (1 L) was stirred at room temperature for 1 h. After removal of the solvent, the residue was taken up in EtOAc (500 ml), washed with water, 1 N HCl and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography eluted with EtOAc-hexanes (25% to 75%) to give 38.7 g (68% yield) of compound **34** as a white solid:

^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9H), 1.40 (s, 9H), 2.58-2.70 (m, 2H), 4.38 (s, 2H), 4.48-4.55 (m, 1H), 4.69 (s, 2H), 4.96 (s, 2H), 5.78-5.80 (m, 1H), 7.20-7.24 (m, 2H), 7.38-7.40 (m, 2H), 7.64-7.66 (d, J = 7.5 Hz, 2H), 8.64-8.66 (d, J = 7.5 Hz, 2H);
MS m/e 580/582 (MH^+); 468/470 [M-(t-Bu)$_2^+$].

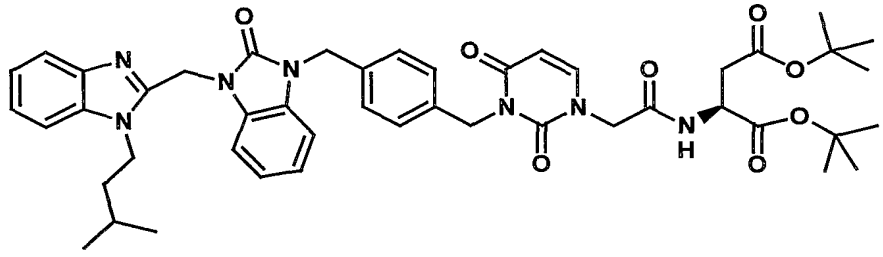
Compound 35



Compound **35** was prepared as described for compound **7** above.

^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.7 Hz, 6H), 1.44 (s, 9H), 1.51-1.74 (m, 3H), 4.32 (s, 2H), 4.43-4.49 (m, 2H), 5.06 (s, 2H), 5.08 (s, 2H), 5.71 (bs, 2H), 5.78 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.99-7.09 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 7.24-7.28 (m, 4H), 7.39-7.44 (m, 4H), 7.95-8.01 (m, 1H);
MS m/e 663 (MH^+).

Compound 36



Compound **36** was prepared in 49% yield using the same procedure of compound **19** with compound **7** and bromide **34**:

^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.7 Hz, 6H), 1.30-1.44 (m, 2H), 1.43 (s, 9H), 1.44 (s, 9H), 1.60-1.65 (m, 1H), 2.69 (dd, J = 4.3Hz, 17.1 Hz, 1H), 2.89 (dd, J = 4.3, 17.1Hz), 4.29 (d, J = 15.8Hz, 1H), 4.27-4.35 (m, 2H), 4.43 (d, J = 15.8Hz, 1H), 4.63-4.66 (m, 1H), 5.05 (s, 2H), 5.06 (s, 2H), 5.49 (s, 2H), 5.49 (s, 2H), 5.77 (d, J = 7.8Hz, 1H), 6.85-6.97 (m, 1H), 6.86-7.00 (m, 1H), 7.14 (d, J = 7.8Hz, 1H), 7.24-7.35 (m, 6H), 7.39 (d, J = 8.3Hz, 2H), 7.49 (d, J = 7.3 Hz, 1H), 7.82-7.84 (m, 1H);
MS m/e 834 (MH^+).

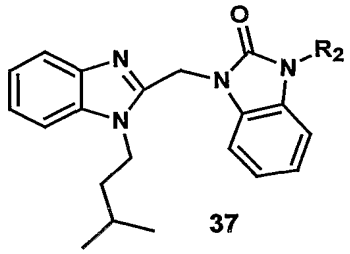


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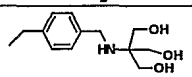
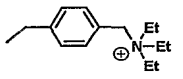
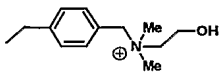
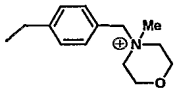
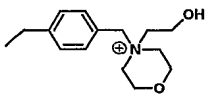
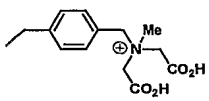
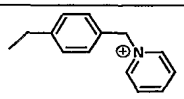
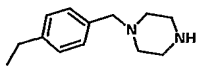
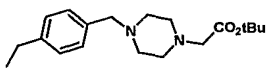
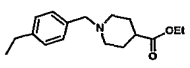
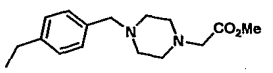
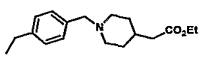
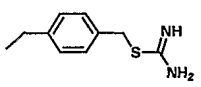
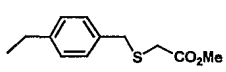
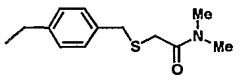
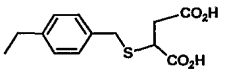
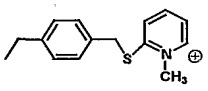
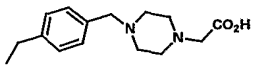
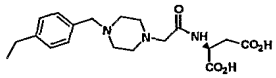
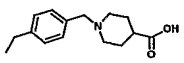
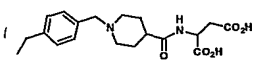
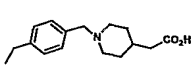
Table 7- Compounds listed below were prepared by treating compound **28** with a nucleophile as described for compound **29**.

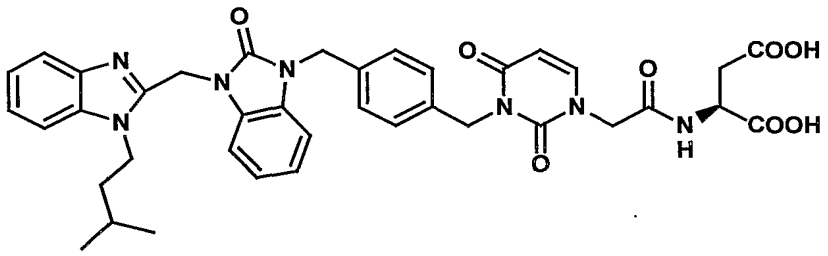
#	R_2	^{1}H-NMR Data	MS Data
37a		(DMSO-d_6) δ 0.93 (d, J = 6.5 Hz, 6H), 1.48-1.53 (m, 2H), 1.63-1.69 (m, 1H), 3.40-3.50 (m, 2H), 4.13-4.19 (m, 3H), 4.32-4.38 (m, 3H), 5.13 (s, 2H), 5.30 (b, 3H), 5.44 (s, 2H), 6.99-7.02 (m, 2H), 7.12-7.15 (m, 1H), 7.18-7.30 (m, 3H), 7.39-7.46 (m, 4H), 7.54-7.60 (m, 2H), 8.38-8.42 (m, 2 H)	558 (MH^+)
37b		(CD_3OD) δ 0.99 (d, J = 6.2 Hz, 6H), 1.42 (t, J = 7.0 Hz, 9H), 1.65-1.77 (m, 3H), 3.21-3.29 (m, 6H), 4.48 (s, 2H), 4.58 (t, J = 7.6 Hz, 2H), 5.25 (s, 2H), 5.76 (s, 2H), 7.17-7.18 (m, 3H), 7.30-7.33 (m, 1H), 7.56-67 (m, 6H), 7.76-7.87 (m, 2H)	538 (MH^+)
37c		(DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6H), 1.43-1.50 (m, 2H), 1.60-1.67 (m, 1H), 2.97 (s, 6H), 3.34-3.40 (m, 2H), 3.84-3.93 (m, 2H), 4.32 (t, J = 8.0 Hz, 2H), 4.54 (s, 2H), 5.17 (s, 2H), 5.31 (t, J = 4.8 Hz, 1H), 5.42 (s, 2H), 7.00-7.05 (m, 2H), 7.15-7.27 (m, 4H), 7.47-7.59 (m, 4H)	526 (MH^+)
37d		(DMSO-d_6) δ 0.92 (d, J= 6.6 Hz, 6H), 1.44-1.51 (m, 2H), 1.61-1.70 (m, 1H), 3.01 (s, 3H), 3.23-3.28 (m, 2H), 3.43-3.55 (m, 2H), 3.83-4.01 (m, 4H), 4.33 (t, J = 8.0 Hz, 2H), 4.64 (s, 2H), 5.18 (s, 2H), 5.42 (s, 2H), 7.00-7.05 (m, 2H), 7.16-7.28 (m, 4H), 7.47-7.59 (m, 6H)	
37e		(DMSO-d_6) δ 0.92 (d, J= 6.6 Hz, 6H), 1.45-1.53 (m, 2H), 1.59-1.70 (m, 1H), 3.56-3.62 (m, 8H), 3.84-3.90 (m, 2H), 3.97-4.01 (m, 2H), 4.35 (t, J = 7.9 Hz, 2H), 4.70 (s, 2H), 5.19 (s, 2H), 5.45 (s, 2H), 7.01-7.05 (m, 2H), 7.18-7.29 (m, 4H), 7.49-7.60 (m, 6H), 8.15 (bs, 2H)	567 (MH^+)
37f		(DMSO-d_6) δ 0.16 (d, J = 6.6 Hz, 6H), 0.73-0.84 (m, 2H), 0.86-0.98 (m, 1H), 3.52 (s, 3H), 3.61-3.69 (m, 2H), 4.07 (s, 4H), 4.15 (bs, 2H), 4.43 (bs, 2H), 4.81 (bs, 2H), 6.28-6.38 (m, 3H), 6.43-6.50 (m, 1H), 6.62-6.80 (m, 6H), 6.84-6.95 (m, 2H)	584 (MH^+)
		(DMSO-d_6) δ 0.88 (d, J = 6.6 Hz, 6H),	516 (MH^+)

37g		1.40-1.48 (m, 2H), 1.58-1.67 (m, 1H), 4.31 (t, J = 8.0 Hz, 2H), 5.11 (s, 2H), 5.41 (s, 2H), 5.81 (s, 2H), 6.98-7.02 (m, 2H), 7.11-7.27 (m, 4H), 7.41-7.58 (m, 6H), 8.12-8.17 (m, 2H), 8.60 (t, J = 7.8 Hz, 1H), 9.17 (d, J = 5.4 Hz, 2H)	
37h		(CD_3OD) δ 0.93 (d, J = 6.6 Hz, 6H), 1.40-1.48 (m, 2H), 1.60-1.72 (m, 1H), 2.38-2.50 (m, 4H), 2.84 (t, J = 5.0 Hz, 4H), 3.50 (s, 2H), 4.33-4.39 (m, 2H), 5.16 (s, 2H), 5.49 (s, 2H), 6.99-7.11 (m, 3H), 7.16-7.21 (m, 1H), 7.26-7.39 (m, 6H), 7.48 (dd, J = 1.3, 6.8 Hz, 1H), 7.65-7.68 (m, 1H)	523 (MH^+)
37i		($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.41-1.49 (m, 2H), 1.46 (s, 9H), 1.66-1.75 (m, 1H), 2.45-2.90 (m, 8H), 3.13 (s, 2H), 4.32 (t, J = 8.1 Hz, 2H), 5.10 (s, 2H), 5.44 (s, 2H), 6.86-6.89 (m, 1H), 6.98-7.04 (m, 2H), 7.25-7.34 (m, 2H), 7.43-7.46 (m, 1H), 7.77-7.82 (m, 1H)	637 (MH^+)
37j		($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.41-1.49 (m, 2H), 1.61-1.87 (m, 7H), 2.21-2.34 (m, 1H), 2.79-2.90 (m, 2H), 3.43-3.54 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 4.32 (t, J = 8.1 Hz, 2H), 5.09 (s, 2H), 5.44 (s, 2H), 6.87-6.90 (m, 1H), 6.97-7.02 (m, 1H), 7.26-7.34 (m, 8H), 7.43-7.47 (m, 1H), 7.77-7.82 (m, 1H)	594 (MH^+)
37k		(CD_3OD) δ 0.99 (d, J = 6.2 Hz, 6H), 1.72-1.74 (m, 3H), 3.31-3.47 (m, 8H), 3.79 (s, 3H), 3.86 (s, 2H), 4.39 (s, 2H), 4.62 (t, J = 6.7 Hz, 2H), 5.23 (s, 2H), 5.83 (s, 2H), 7.20-7.21 (m, 3H), 7.34-7.36 (m, 1H), 7.53-7.61 (m, 4H), 7.68-7.73 (m, 2H), 7.78-7.82 (m, 1H), 7.94-7.97 (m, 1H)	595 (MH^+)
37l		($CDCl_3$) δ 0.95 (d, J = 6.5 Hz, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.41-1.49 (m, 3H), 1.68-1.77 (m, 5H), 1.94-2.05 (m, 2H), 2.23 (d, J = 6.9 Hz, 2H), 2.79-2.92 (m, 2H), 3.47-3.58 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 4.29-4.35 (m, 2H), 5.10 (s, 2H), 5.45 (s, 2H), 6.88-6.91 (m, 1H), 6.99-7.02 (m, 2H), 7.28-7.45 (m, 7H), 7.80-7.83 (m, 1H), 8.52-8.54 (m, 1H)	608 (MH^+)
37 m		(DMSO-d_6) δ 0.90 (d, J = 6.5 Hz, 6H), 1.48-1.53 (m, 2H), 1.63-1.69 (m, 1H), 3.38-3.48 (m, 4H), 4.28-4.33 (m, 2 H), 4.42 (s, 2H), 4.57 (t, J = 5.4 Hz, 2H), 5.10 (s, 2H), 5.41 (s, 2H), 6.98-7.01 (m, 2H), 7.12-7.24 (m, 4H), 7.39-7.46 (m, 4H), 7.50-7.54 (m, 2H), 7.57-7.59 (m, 2H), 8.99 (b, 4H)	513 (MH^+)
37n		(DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6H), 1.42-1.47 (m, 2H), 1.61-1.67 (m, 1H), 3.20 (s, 2H), 3.57 (s, 3H), 3.77 (s, 2H), 4.30-4.34 (m, 2H), 5.10 (s, 2H), 5.42 (s, 2H), 6.98-7.01 (m, 2H), 7.14-7.18 (m, 2H), 7.20-7.27 (m, 4H), 7.31-7.33 (m, 2H), 7.51 (d, J = 4.8, 1H), 7.60 (d, J = 4.7, 1H)	543 (MH^+)

37o		(DMSO-d_6) δ 0.91 (d, J = 3.9, 6H), 1.42-1.46 (m, 2H), 1.61-1.69 (m, 1H), 2.78 (s, 3H), 2.91 (s, 3H), 3.73 (s, 2H), 4.31-4.33 (m, 2H), 5.09 (s, 2 H), 5.42 (s, 2H), 6.99-7.01 (m, 2H), 7.14-7.33 (m, 8H), 7.51 (d, J = 4.8, 1H), 7.60 (d, J = 4.7, 1H)	556 (MH^+)
37p		(CD_3OD) δ 0.91 (d, J = 6.5 Hz), 1.37-1.44 (m, 2 H), 1.59-1.71 (m, 1 H), 2.46-2.55 (m, 1 H), 2.79-2.87 (m, 1 H), 3.68 (t, J = 7.4 Hz, 1 H), 3.88 (s, 2 H), 4.34 (t, J = 8.0 Hz, 2 H), 5.14 (s, 2 H), 5.49 (s, 2 H), 7.01-7.09 (m, 3 H), 7.16-7.19 (m, 1 H), 7.28-7.38 (m, 6 H), 7.45-7.49 (m, 1 H), 7.65-7.68 (m, 1 H)	587 (MH^+)
37q		(CD_3OD) δ 0.95 (d, J = 6.6 Hz, 6H), 1.44-1.52 (m, 2H), 1.65-1.73 (m, 1H), 4.21 (s, 3H), 4.38 (t, J = 8.2 Hz, 2H), 4.71 (s, 2H), 5.19 (s, 2H), 5.51 (s, 2H), 7.04-7.09 (m, 3H), 7.17-7.22 (m, 1H), 7.28-7.37 (m, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.50-7.55 (m, 3H), 7.65-7.73 (m, 2H), 8.05 (d, J = 8.3 Hz, 1H), 8.31 (t, J = 8.1 Hz, 1H), 8.79 (d, J = 5.8 Hz, 1H)	562 (MH^+)
37r		(DMSO-d_6) δ 0.90 (d, J = 6.5 Hz, 6H), 1.51-1.58 (m, 2H), 1.63-1.69 (m, 1H), 3.11-3.24 (m, 2H), 3.27-3.40 (m, 2H), 3.75-3.83 (m, 2H), 4.20-4.29 (m, 2H), 4.41-4.47 (m, 2H), 5.14 (s, 2H), 5.63 (s, 2H), 7.05-7.07 (m, 2H), 7.18-7.21 (m, 1H), 7.31-7.35 (m, 1H), 7.42-7.51 (m, 4H), 7.56 (d, J = 7.4 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 6.9 Hz, 1H)	581 (MH^+)
37s		(CD_3OD) δ 0.93 (d, J = 6.5 Hz, 6H), 1.40-1.48 (m, 2H), 1.62-1.71 (m, 1H), 2.54-2.70 (m, 10H), 2.92-3.10 (m, 2H), 3.53 (s, 2H), 4.36 (t, J = 8.1 Hz, 2H), 4.53 (t, J = 6.8 Hz, 1H), 5.17 (s, 2H), 5.50 (s, 2H), 7.00-7.10 (m, 3H), 7.17-7.20 (m, 1H), 7.26-7.40 (m, 6 H), 7.47-7.50 (m, 1H), 7.66-7.68 (m, 1 H)	696 (MH^+)
37t		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.42-2.30 (10H), 2.64-2.75 (m, 2H), 3.31-3.45 (m, 2H), 4.31 (t, J = 8.0 Hz, 2H), 5.10 (bs, 2H), 5.41 (s, 2H), 6.98-7.01 (m, 2H), 7.14-7.26 (m, 8H), 7.50 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H)	566 (MH^+)
37u		(CD_3OD) δ 0.92 (d, J = 6.6 Hz, 6H), 1.38-1.47 (m, 2H), 1.63-1.68 (m, 1H), 1.70-1.83 (m, 4H), 2.00-2.10 (m, 2H), 2.16-2.25 (m, 1H), 2.66 (d, J = 6.0 Hz, 2H), 2.84-2.93 (m, 2H), 3.50 (bs, 2H), 4.36 (t, J = 8.3 Hz, 2H), 4.47 (t, J = 5.8 Hz, 1H), 5.17 (s, 2H), 5.50 (s, 2H), 7.03-7.09 (m, 3H), 7.17-7.20 (m, 1H), 7.29-7.38 (m, 6H), 7.48 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 7.1 Hz, 1H)	681 (MH^+)
37v		(DMSO-d_6) δ 0.89 (d, J = 6.6 Hz, 6H), 1.07-1.23 (m, 2H), 1.40-1.47 (m, 2H), 1.58-1.69 (m, 4H), 1.80-1.94 (m, 2H), 2.11 (d, J = 6.2 Hz, 2H), 2.67-2.75 (m, 2H), 3.32-3.38 (m, 2H), 4.31 (t, J = 7.9 Hz, 2H), 5.09 (s, 2H), 5.41 (s, 2H),	580 (MH^+)

		6.98-7.01 (m, 2H), 7.14-7.32 (m, 8H), 7.50 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H)	

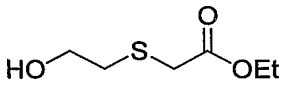
Compound 38



The t-butyl groups of ester **35** were removed with 4N HCl in dioxane using the procedure described for **32**. The acid was then treated with 2 equivalents of 1 N NaOH in MeOH to provide a di-sodium salt of **38**:

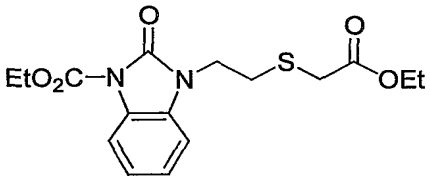
^{1}H NMR (CD_3OD) δ 0.82 (d, J = 6.6 Hz, 6H), 1.29-1.37 (m, 2H), 1.51-1.57 (m, 1H), 2.60-2.63 (m, 2H), 4.23-4.28 (m, 2H), 4.40-4.53 (m, 3H), 5.00 (s, 2H), 5.06 (s, 2H), 5.40 (s, 2H), 5.67 (d, J = 8.1 Hz, 1H), 6.93-7.10 (m, 4H), 7.07-7.10 (m, 1H), 7.18-7.30 (m, 6H), 7.40 (d, J = 6.9 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 6.9 Hz, 1H);
IR (KBr, cm^{-1}) 3422, 2957, 1705, 1662, 1612, 1493, 1456, 1407, 747;
MS m/e 722 (MH^+).

Compound 39



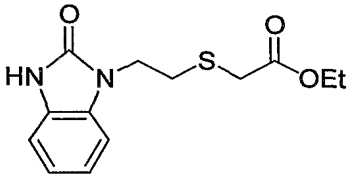
Mercaptoethanol (3 g, 38.39 mmol) and K_2CO_3 (6.36 g, 46.01 mmol) were suspended in acetone (50 ml). Ethylbromoacetate (7.05 g, 42.21 mmol) was added. The resulting mixture was stirred at room temperature overnight. It was filtered and the filtrate was evaporated to give 6 g (95 % yield) of compound **39** as a yellow oil.

Compound 40



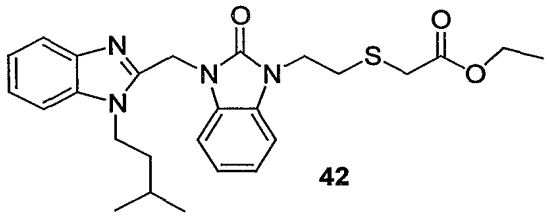
DEAD (506.77 mg, 2.9 mmol) was added to a stirred mixture of 2-oxo-2,3-dihydro-benzoimidazole-1-carboxylic acid ethyl ester (500 mg 2.42 mmol) (Meanwell et al, *J.Org. Chem.* **1995**, 60, 1565-1582.), PPh_3 (763.21 mg, 2.90 mmol), and (2-hydroxy-ethylsulfanyl)-acetic acid ethyl ester (497.75 mg, 3.03 mmol) in dry THF (20 ml) at room temperature. The mixture was stirred for 48 hours. The solvent was removed and the residue purified by column chromatography (25 % EtOAc/Hexane) to give 422 mg (49% yield) of the desired compound **40**.

Compound 41



Compound **40** (400 mg, 1.13 mmol) in THF (5 ml) was stirred with 21%NaOEt in EtOH (23.15 mg, 0.43 mmol) at room temperature overnight. The mixture was evaporated to give 284 mg (89 % yield) of compound **41**.

Compound 42

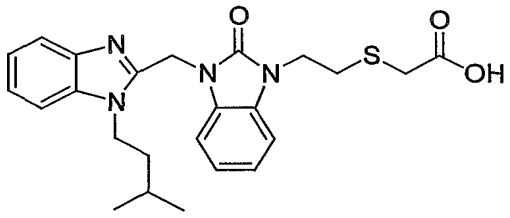


42

Compound **42** was prepared as with [2-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-ethylsulfanyl]-acetic acid ethyl ester and compound **6** as described for compound **7**.

^{1}H NMR (DMSO-d_6) δ 0.90 (d, J = 6.6, 6 H), 1.18 (t, J = 7.1, 3 H), 1.37-1.44 (m, 2 H), 1.59-1.65 (m, 1 H), 2.94 (t, J = 6.8, 2 H), 3.45 (s, 2 H), 4.01-4.13 (m, 4 H), 4.26-4.32 (m, 2 H), 5.36 (s, 2 H), 6.98-7.08 (m, 2 H), 7.14-7.28 (m, 4H), 7.48 (d, J = 7.4, 2H), 7.59 (d, J = 7.4, 2H);
MS m/e 481 (MH^+).

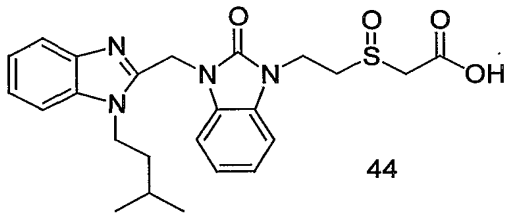
Compound 43



Compound **42** (110 mg, 0.23 mmol) was dissolved in MeOH (10 ml). 1N NaOH (13.73 mg, 0.34 mmol) was added. The reaction was stirred overnight then the solvent was removed. The residue was adjusted to pH 5 with 1N HCl. The white precipitate was filtered, washed with water and dried under vacuum to give 54 mg (52% yield) of compound **43** as a white solid.

^{1}H NMR (DMSO-d_6) δ 0.89 (d, J = 6.6, 6H), 1.34-1.39 (m, 2H), 1.59-1.65 (m, 1H), 2.81 (t, J = 7.1, 2H), 3.01 (s, 2H), 4.08 (t, J = 6.8, 2H), 4.28 (t, J = 8.0, 2H), 5.35 (s, 2H), 6.95-7.05 (m, 2H), 7.14-7.25 (m, 3H), 7.38 (d, J = 6.9, 1H), 7.48 (d, J = 7.6, 1H), 7.59 (d, J = 7.4, 1H);
MS m/e 453 (MH^+).

Compound 44

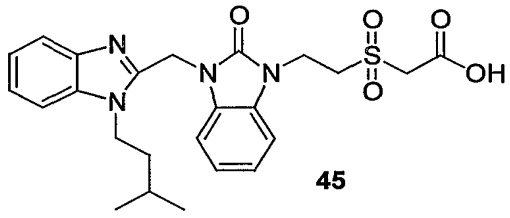


44

Compound **43** (100 mg, 0.22 mmol) was dissolved in acetic acid (7 ml). Sodium perborate tetrahydrate (37.39 mg, 0.24 mmol) was added The mixture was heated at 50°C overnight. Then the acetic acid was removed. The residue was taken into water and acidified with 1N HCl to pH 5. The product was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and evaporated to give 63 mg (61% yield) of the compound **44.**

^{1}H NMR (DMSO-d_6) δ 0.88 (d, J = 6.6, 6 H), 1.23 (t, J = 7.1, 2 H), 1.32-1.39 (m, 2 H), 1.56-1.65 (m, 2 H), 3.16 (s, 1 H), 3.88-3.95 (m, 1 H), 4.25-4.32 (m, 2 H), 5.35 (s, 2 H), 6.97-7.08 (m, 2 H), 7.14-7.29 (m, 4 H), 7.48 (d, J = 7.4, 1H), 7.59 (d, J = 7.0, 1H);
MS m/e 469 (MH^+).

Compound 45

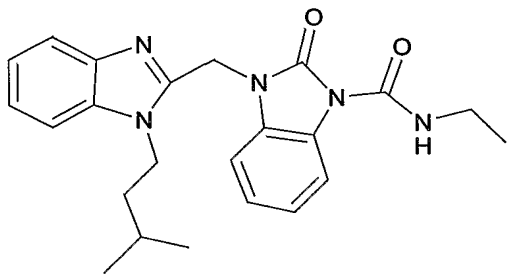


45

Compound **44** (110 mg, 0.24 mmol) was dissolved in acetic acid (7 ml). Sodium perborate tetrahydrate (149.58 mg, 0.97 mmol) was added and the mixture heated at 55 °C overnight. Acetic acid was removed and the residue taken into water and acidified with 1N HCl to pH 5. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and evaporated to give 63 mg (53% yield) of compound **45** as a white solid.

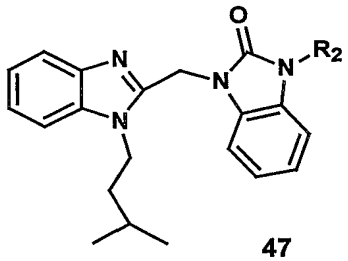
^{1}H NMR (DMSO-d_6) δ 0.90 (d, J = 5.0, 6H), 1.35-1.51 (m, 2H), 1.56 (s, 2H), 1.60-1.70 (m, 2H), 3.70-3.75 (m, 2H), 4.28-4.33 (m, 3H), 5.35 (s, 2H), 6.98-7.06 (m, 2H), 7.13-7.26 (m, 4H), 7.47-7.51 (m, 1H), 7.56-7.62 (m, 2H);
MS m/e 485 (MH^+).

Compound 46



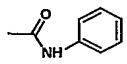
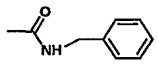
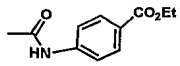
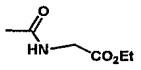
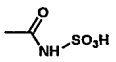
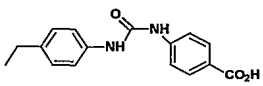
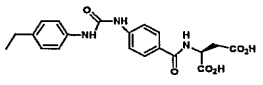
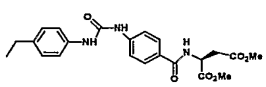
A solution of compound **6** (50 mg, 0.15 mmol) and triethylamine (15 mg, 0.15 mmol) in DMF (2 mL) was cooled to 0°C. To this solution was added ethyl isocyanate (11 mg, 0.15 mmol) and the resulting mixture was stirred at 0°C for 4 hours. The reaction mixture was diluted with EtOAc, washed with H_2O, and dried over $MgSO_4$. Purification by flash column chromatography (straight EtOAc) gave 30 mg (49% yield) of compound **46**:

^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.7 Hz, 6H), 1.28 (t, J = 7.3 Hz, 3H), 1.32-1.40 (m, 2H), 1.63-1.72 (m, 1H), 3.44-3.54 (m, 2H), 4.24-4.30 (m, 2H), 5.46 (s, 2H), 7.13-7.18 (m, 2H), 7.31-7.32 (m, 3H), 7.45-7.54 (m, 1H), 7.80-7.83 (m, 1H), 8.18-8.21 (m, 1H), 8.63-8.70 (m, 1H);
MS m/e 406 (MH^+).



47

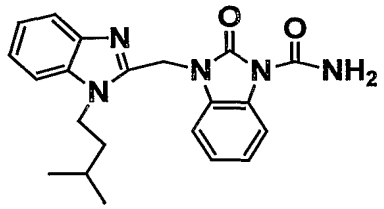
Table 8 - The compounds were prepared from compound **6** and commercially available isocyanates using the method above.

#	R_2	^{1}H-NMR Data	MS Data
47a		($CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 6H), 1.42-1.50 (m, 2H), 1.67-1.78 (m, 1H), 4.29-4.35 (m, 2H), 5.48 (s, 2H), 7.18-7.23 (m, 3H), 7.29-7.36 (m, 3H), 7.43 (t, J = 7.9 Hz, 2H), 7.52-7.55 (m, 1H), 7.63-7.68 (m, 2H), 7.80-7.84 (m, 1H), 8.27-8.33 (m, 1H), 10.88 (s, 1H)	No data
47b		($CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 6H), 1.29-1.38 (m, 2H), 1.58-1.69 (m, 1H), 4.19-4.25 (m, 2H), 4.65 (d, J = 5.8 Hz, 2H), 5.39 (s, 2H), 7.12-7.16 (m, 2H), 7.27-7.38 (m, 8H), 7.42-7.46 (m, 1H), 7.77-7.80 (m, 1H), 8.20-8.23 (m, 1H), 9.11-9.16 (m, 1H)	468 (MH^+)
47c		($CDCl_3$) δ 0.97 (d, J = 6.7 Hz, 6H), 1.42 (t, J = 7.1 Hz, 3H), 1.43-1.51 (m, 2H), 1.68-1.77 (m, 1H), 4.28-4.34 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 5.46 (s, 2H), 7.20-7.25 (m, 2H), 7.28-7.33 (m, 3H), 7.53-7.56 (m, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.78-7.82 (m, 1H), 8.10 (d, J = 8.7 Hz, 2H), 8.26-8.29 (m, 1H), 11.14 (s, 1H)	526 (MH^+)
47d		($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 6H), 1.33 (t, J = 7.1 Hz, 3H), 1.39-1.47 (m, 2H), 1.64-1.75 (m, 1H), 4.00 (d, J = 5.3 Hz, 1H), 4.18-4.32 (m, 5H), 5.42 (s, 2H), 7.13-7.19 (m, 2H), 7.28-7.35 (m, 3H), 7.46-7.52 (m, 1H), 7.77-7.81 (m, 1H), 8.14-8.20 (m, 1H), 9.30 (t, J = 5.3 Hz, 1H)	464 (MH^+)
47e		(DMSO-d_6) δ 0.98 (d, J = 6.2 Hz, 6H), 1.67-1.77 (m, 3H), 4.51 (t, J = 7.9 Hz, 2H), 5.75 (s, 2H), 7.20-7.28 (m, 2H), 7.33-7.40 (m, 1H), 7.46-7.56 (m, 2H), 7.71 (d, J = 7.3 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.09-8.14 (m, 1H), 10.18 (s, 1H)	456 (MH^+)
47f		(DMSO-d_6) δ 0.91 (d, J = 6.6 Hz, 6H), 1.41-1.48 (m, 2H), 1.63-1.67 (m, 1H), 4.34 (t, J = 7.7 Hz, 2H), 5.05 (s, 2H), 5.46 (s, 2H), 6.87 (s, 1H), 7.01 (t, J = 3.7 Hz, 2H), 7.15-7.33 (m, 5H), 7.42 (d, J = 8.6 Hz, 2H), 7.52-7.64 (m, 4H), 7.85 (d, J = 8.7 Hz, 2H), 8.96 (s, 1H), 9.20 (s, 1H)	603 (MH^+)
47g[a]		(CD_3OD) δ 0.90 (d, J = 6.6 Hz, 6H), 1.36-1.48 (m, 2H), 1.57-1.69 (m, 1H), 2.73-2.88 (m, 2H), 4.27-4.42 (m, 2H), 4.61-4.74 (m, 1H), 5.11 (s, 2H), 5.47 (s, 2H), 7.00-7.14 (m, 4H), 7.26-7.32 (m, 4H), 7.35-7.52 (m, 5H), 7.63-7.66 (m, 1H), 7.83 (d, J = 8.7 Hz, 2H),	718 (MH^+)
47h[b]		(DMSO-d_6) δ 0.91 (d, J = 6.5 Hz, 6H), 1.41-1.48 (m, 2H), 1.60-1.67 (m, 1H), 2.77-2.98 (m, 2H), 3.61 (s, 3H), 3.64 (s, 3H), 4.32 (t, J = 7.8 Hz, 2H), 4.78-4.85 (m, 1H), 5.05 (s, 2H), 5.42 (s, 2H), 6.99-7.02 (m, 2H), 7.15-7.24 (m, 4H), 7.31 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz,	746 (MH^+)

		2H), 7.52 (d, J = 8.9 Hz, 3H), 7.60 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 8.74-8.77 (m, 2H), 8.94 (s, 1H)	

a, hydrolysis of **47a** as described for compound **8**; **b**, amide bond formation as described for compound **9**.

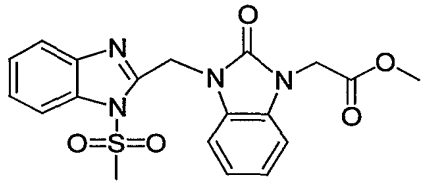
Compound 48



Compound **47e** (100 mg, 0.22 mmol) was heated at 100 °C for 2 hours in a mixture of DMF (10 ml) and H_2O (30 mL). The aqueous reaction mixture was extracted with EtOAc. The organic extracts were dried over $MgSO_4$, evaporated, and purified by flash column chromatography (straight EtOAc) to give 18 mg (22% yield) of compound **48**:

^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 6H), 1.38-1.46 (m, 2H), 1.68-1.76 (m, 1H), 4.28-4.33 (m, 2H), 5.49 (m, 2H), 7.17-7.28 (m, 2H), 7.33-7.35 (m, 2H), 7.53-7.56 (m, 1H), 7.82-7.86 (m, 1H), 8.18-8.21 (m, 1H), 8.63 (bs, 1H).

Compound 49



Compound **49** was prepared from compound **2** and (2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid methyl ester (Meanwell et al, *J.Org. Chem.* 1995, 60, 1565-1582.) as described for compound **3** without treatment with tetrabutylammonium fluoride hydrate.

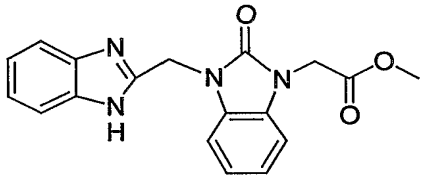
^{1}H NMR ($CDCl_3$) δ 3.41 (s, 3H), .77 (s, 3H), 4.65 (s, 2H), 5.57 (s, 2H), 6.92-7.11 (m, 1H), 7.11-7.27 (m, 3H), 7.32-7.46 (m, 3H), 7.66 (d, J = 9.0 Hz, 1H), 7.67-7.83 (m, 1H), 7.88 (d, J = 9.0 Hz, 1H);

MS m/e 414 (MH+);

Anal. Calcd for $C_{19}H_{18}N_4O_5S$: C, 55.07; H, 4.38; N, 13.52

Found: C, 55.38; H, 4.58; 13.64.

Compound 49a

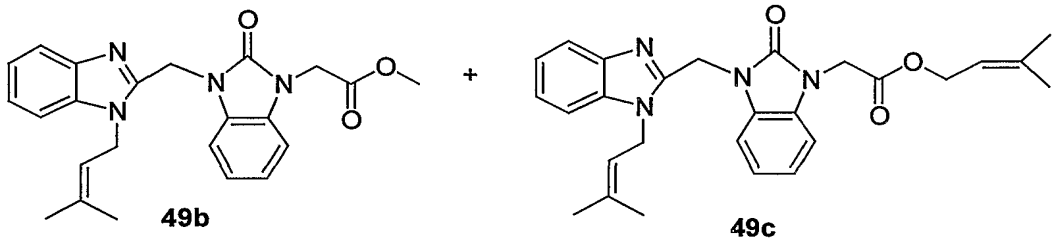


Compound **49** (3 g, 7.23 mmol) and tetrabutylammonium fluoride (1.89 g, 7.23 mmol) were refluxed in THF (300 ml) for 3 hours. After cooling, the solvent was evaporated. The residue was diluted with water and extracted with diethyl ether and EtOAc. The combined organic extracts were dried over Na_2SO_4, and evaporated to give 2.3 g (96% yield) of the desired compound **49a** as a yellow solid.

^{1}H NMR (DMSO-d6) δ 3.61 (s, 3H), 4.79 (s, 2H), 5.29 (s, 2H), 7.00-7.21 (m, 6H), 7.43 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H).

MS m/e 336 (MH^+).

Compound 49a and 49b



49b **49c**

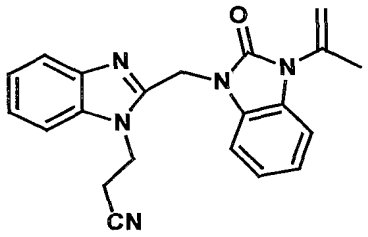
To compound **49a** (300 mg, 1.02 mmol) in DMF (10 ml) was added NaH (60% in mineral oil, 45.2 mg, 1.13 mmol) at room temperature. After stirring for 1 hour, 1-bromo-3-methyl-2-butene (168.42 mg, 1.13 mmol) was added and the mixture was stirred overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (hexane/EtOAc = 4:1) to afford 76 mg (18% yield) of compound **49b** and 120 mg (25% yield) of compound **49c** both as a white solids.

Compound 49b:

^{1}H NMR (DMSO-d6) δ 1.65 (s, 3H), 1.86 (s, 3H), 3.70 (s, 3H), 4.80 (s, 2H), 4.95-4.98 (m, 2H), 5.03-5.05 (m, 1H), 5.38 (s, 2 H), 7.01-7.08 (m, 2H), 7.15-7.25 (m, 4H), 7.43 (d, J = 7.5, 1H), 7.59 (d, J = 7.4, 1H);

MS m/e 405 (MH^+).

Compound 50



To compound **3** (1.5 g, 4.929 mmol) suspended in CH_3CN (30 ml) was added acrylonitrile (523 mg, 9.858 mmol) followed by MTBD (38 mg, 0.246 mmol). The reaction mixture was heated at 50-60 °C for 16 hours. The solution became transparent. The solvent was stripped. The yellow oil residue was taken up in ether and triturated to give 1.67 g of compound **50** as a pale yellow solid:

^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.75 (t, J = 6.7 Hz, 2H), 4.82 (t, J = 6.7 Hz, 2H), 5.24 (s, 1H), 5.41 (s, 1 H), 5.45 (s, 2H), 7.11-7.16 (m, 3H), 7.31-7.37 (m, 3H), 7.57-7.60 (m, 1H), 7.81-7.85 (m, 1H);

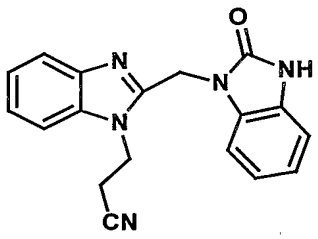
IR (KBr, cm^{-1}) 3005, 1686, 1655, 1615, 1508, 1487, 1427, 1400, 745;

MS m/e 358 (MH^+);

Anal. Calcd for $C_{21}H_{19}N_5O$: C, 70.57; H, 5.36; N, 19.59

Found: C, 70.42; H, 5.51; N, 19.61

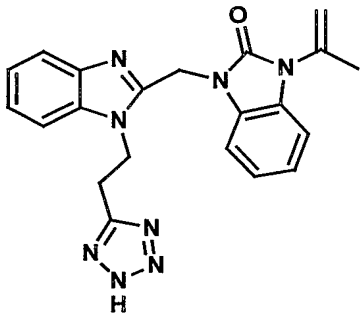
Compound 51



Compound **51** was prepared as described for compound **6**.

^{1}H NMR (DMSO-d6) δ 3.20 (t, J = 6.7 Hz, 2H), 4.89 (t, J = 6.8 Hz, 2H), 5.60 (s, 2H), 6.97-7.08 (m, 3H), 7.27 (d, J = 6.6 Hz, 1H), 7.39-7.50 (m, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 11.20 (s, 1H).

Compound 52



Nitrile **50** (9.19 g, 25.71 mmol), ammonium chloride (4.13 g, 77.13 mmol) and sodium azide (5.01 g, 77.13 mmol) were stirred in DMF (100 mL) at 100 °C for two days. The solvent was evaporated and the residue diluted with water and the pH was adjusted to 5 with concentrated HCl and the solid was filtered. The collected solid was triturated with hot methanol to give 8.85 g (86% yield) of compound **52** as a solid. To the suspension of the tetrazole (6.30 g) in methanol was added 1 equivalent of 1 N NaOH. The suspension was then heated to dissolve the solid and solvent was evaporated. The residue was dried in vacuum and triturated in ether to give 6.36 g of the sodium salt of compound **52**:

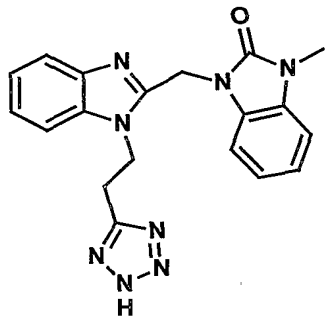
^{1}H NMR (DMSO-d_6) δ 2.15 (s, 3H), 3.43 (t, J = 7.1 Hz, 2H), 4.84 (t, J = 7.1 Hz, 2H), 5.20 (s, 1H), 5.38 (s, 2H), 5.40 (d, *J* = 1.2 Hz, 1H), 7.04-7.09 (m, 2H), 7.16-7.26 (m, 4H), 7.53-7.58 (m, 2H);
IR (KBr, cm^{-1}) 3407, 2484, 2115, 1701, 1656, 1613, 1487, 1396, 1156, 751.

MS m/e 401 (MH^+);

Anal. Calcd for $C_{21}H_{20}N_8O$: C, 62.99; H, 5.03; N, 27.98

Found: C, 59.91; H, 5.20; N, 28.30

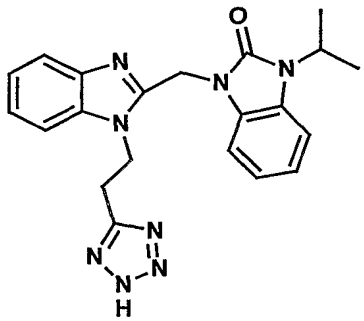
Compound 53



Compound **53** was prepared as described for compound **52** except 1-methyl-2-benzimidazolone was used in the coupling step.

^1H NMR (CD_3OD) δ 3.33 (t, J = 6.9Hz, 2H), 3.46 (s, 3H), 4.79 (t, J = 6.9 Hz, 2H), 5.21 (s, 2H), 6.99 (d, J = 7.0Hz ,1H), 7.07-7.31 (m, 5H), 7.50-7.54 (m, 2H);
MS m/e 375 (MH^+);

Compound 54



To a solution of compound **52** (2.0 g, 4.99 mmol) and 1 N NaOH (4.99 mmol) in methanol (20 mL) was added 10% Pd/C (0.5 g). The mixture was hydrogenated on a Parr shaker for 3 days. The catalyst was removed by filtration. The filtrate was evaporated, and the residue was purified using C18 column chromatography (H_2O: MeOH(1% TFA) = 10:1 to 10 :6 as eluant) to give 1.52 g (72% yield) of compound **54** as a white solid:

^{1}H NMR ($CDCl_3$) δ 1.46 (d, J = 7.0 Hz, 6 H), 3.10 (t, J = 6.6 Hz, 2 H), 4.58-4.71 (m, 1 H), 4.68 (t, J = 6.6 Hz, 2 H), 5.13 (s, 2 H), 6.94-7.22 (m, 5 H), 7.31 (d, J = 7.9 Hz, 1 H), 7.49 (t, J = 8.6 Hz, 2 H);

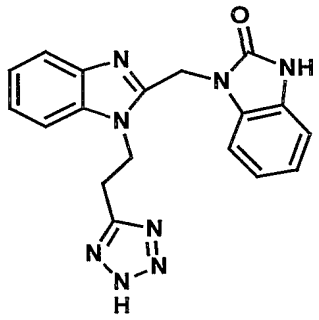
IR (KBr, cm^{-1}) 3384, 1696, 1490, 1410, 751.

MS m/e 403 (MH^+);

Anal. Calcd for $C_{21}H_{22}N_8O \cdot H_2O$ C, 57.01; H, 5.24; N, 25.33

Found: C, 56.78; H, 5.62; N, 24.93

Compound 55

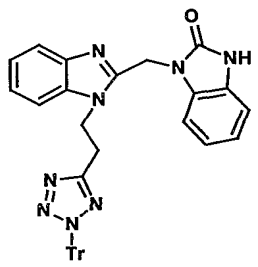


Compound **55** was prepared from compound **52** as described for compound **6**.

^{1}H NMR (CD_3OD) δ 3.78 (t, J = 6.6 Hz, 2H), 5.19 (t, J = 6.6Hz, 2H), 5.89 (s, 2H), 7.14-7.21 (m, 3H), 7.31-7.35 (m, 1H), 7.62-7.74 (m, 3H), 7.98 (dd, J = 1.6, 7.0Hz, 1H);

MS m/e 361 (MH^+).

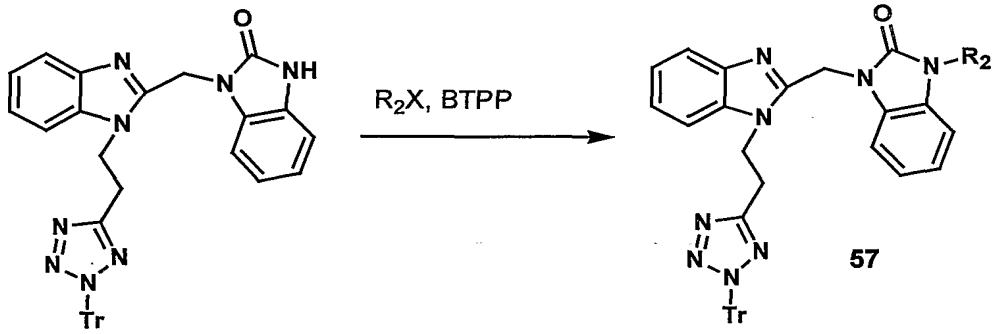
Compound 56



Compound **55** (31.3 g, 86.85mmol), triethylamine (13.19 mmol) and trityl chloride (26.64 mmol) were mixed in DMF (0.5 mL) and were stirred at 70 °C for 16 hours. To the mixture additional triethylamine (13.19 g) and trityl chloride (9.52 g) were added and the resulting mixture was stirred for an additional 2 hours. The solvent was evaporated, and the residue was triturated in 1 N NaOH solution and filtered. The solid collected was triturated in hot methanol, cooled to room temperature and filtered to give 44.0 g (84% yield) of compound **56** as a white powder. The filtrate was concentrated to give additional 4.1 g (8% yield) of compound **56**.

^{1}H NMR (DMSO-d_6) δ 3.46 (t, J = 6.3 Hz, 2H), 4.82 (t, J = 6.3 Hz, 2H), 5.15 (s, 2H), 6.81-7.14 (m, 12H), 7.27-7.37 (m, 10H), 7.56 (dd, J = 1.5, 6.7 Hz, 1H);
MS m/e 625 (MH^+);
Anal. Calcd for $C_{37}H_{30}N_8O$: C, 73.74; H, 5.02; N, 18.59
Found: C, 73.46; H, 5.07; N, 18.31.

Compound 57 (General Method)



Compound **56** (500 mg, 0.83 mmol) was suspended in THF (15 mL) or THF/DMF (10 mL / 2 mL) and the base BTPP (518 mg, 1.66 mmol, 2 eq) was added

at room temperature. This solution was allowed to stir for 15-30 minutes at which time the alkyl or benzyl halide (0.91 mmol, 1.1 eq) was added. The reaction was stirred 16 hours at room temperature under N_2 atmosphere. The solvent was evaporated and the resulting residue was taken up in water and extracted with ether, ethyl acetate, or methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by flash chromatography on silica gel using a mixture of solvents such as ethyl acetate, hexanes, methylene chloride and methanol.

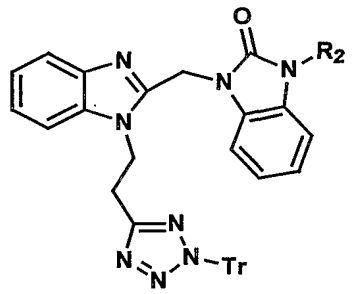
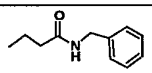
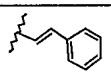
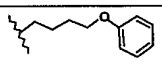
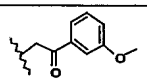
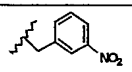
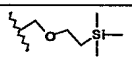
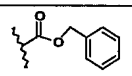
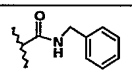


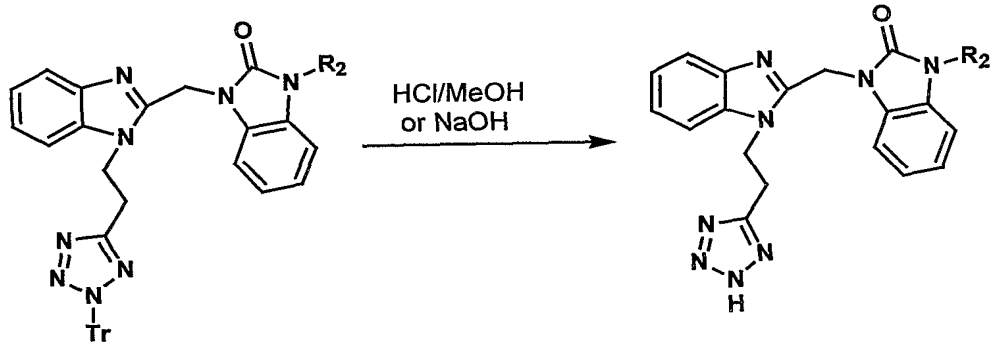
Table 9 – Alkylation of compound 56 with alkyl halide as described above.

#	R_2	^{1}H-NMR Data	MS Data
57a	$CH_2CH_2CO_2Et$	(DMSO-d6) 2.56 (t, J = 6.9 Hz, 2 H), 3.41 (t, J = 6.3 Hz, 2 H), 4.07 (t, J = 6.6 Hz, 2 H), 4.19 (d, J = 5.9 Hz, 2 H), 4.79 (t, J = 6.7 Hz, 2 H), 5.20 (s, 2 H), 6.82-6.93 (m, 7 H), 6.99-7.22 (m, 9 H), 7.27-7.36 (m, 11 H), 7.56-7.58 (m, 1 H), 8.49 (t, J = 5.8 Hz, 1 H)	764 (MH+)
57b		(DMSO-d6) 2.56 (t, J = 6.9 Hz, 2 H), 3.41 (t, J = 6.3 Hz, 2 H), 4.07 (t, J = 6.6 Hz, 2 H), 4.19 (d, J = 5.9 Hz, 2 H), 4.79 (t, J = 6.7 Hz, 2 H), 5.20 (s, 2 H), 6.82-6.93 (m, 7 H), 6.99-7.22 (m, 9 H), 7.27-7.36 (m, 11 H), 7.56-7.58 (m, 1 H), 8.49 (t, J = 5.8 Hz, 1 H)	764 (MH+)
57c	CH_2OCH_3	(DMSO-d6) 3.23 (s, 3 H), 3.45 (t, J = 6.6 Hz, 2 H), 4.82 (t, J = 6.6 Hz, 2 H), 5.22 (s, 2 H), 5.26 (s, 2 H), 6.82-6.85 (m, 6 H), 6.97 (dd, J =1.1, 7.7 Hz, 1 H), 7.02-7.16 (m, 3 H), 7.22-7.35 (m, 12 H), 7.55 (dd, J = 2.4, 7.6 Hz, 1 H)	647 (MH+)
57d		(CDCl3) 3.26 (t, J = 6.9 Hz, 2 H), 4.56 (d, J = 6.0 Hz, 2 H), 4.82 (t, J = 6.9 Hz, 2 H), 5.27 (s, 2 H), 6.15-6.25 (m, 1 H), 6.53, 6.58 (bs, 1 H), 6.90-6.99 (m, 9 H), 7.12-7.39 (m, 18 H), 7.76 (d, J = 7.9 Hz, 1 H)	719 (MH+)
57e		(CDCl3) 1.77-1.94 (m, 4 H), 3.27 (t, J = 6.8 Hz, 2 H), 3.88 (t, J = 6.9 Hz, 2 H), 3.94 (t, J = 6.0 Hz, 2 H), 4.80 (t, J = 6.8 Hz, 2 H), 5.24 (s, 2 H), 6.83 (dd, J = 1.0, 8.7 Hz, 2 H), 6.90-7.01 (m, 11 H), 7.12-7.37 (m, 14 H), 7.75 (d, J = 8.0 Hz, 1 H)	

57f		(CDCl3) 3.28 (t, J = 6.8 Hz, 2 H), 3.83 (s, 3 H), 4.76 (t, J = 6.9 Hz, 2 H), 5.20 (s, 2 H), 5.30 (s, 2 H), 6.76-6.77 (m, 1 H), 6.90-7.00 (m, 8 H), 7.14-7.38 (m, 15 H), 7.49-7.60 (m, 2 H), 7.77 (d, J = 8.0 Hz, 1 H)	751 (MH+)
57g		(CDCl3) 3.27 (t, J = 7.0 Hz, 2 H), 4.83 (t, J = 7.0 Hz, 2 H), 5.02 (s, 2 H), 5.30 (s, 2 H), 6.77-6.79 (m, 1 H), 6.94-7.00 (m, 8 H), 7.18-7.39 (m, 12 H), 7.41-7.47 (m, 2 H), 7.58 (d, J = 7.4 Hz, 1 H), 7.77 (d, J = 7.9 Hz, 1 H), 8.09-8.12 (m, 2 H)	738 (MH+)
57h		(CDCl3) 0.02 (s, 9 H), 0.91 (t, J = 8.1 Hz, 2 H), 3.30 (t, J = 6.8 Hz, 2 H), 3.59 (t, J = 8.3 Hz, 2 H), 4.82 (t, J = 6.9 Hz, 2 H), 5.22 (s, 2 H), 5.26 (s, 2 H), 6.93-6.97 (m, 6 H), 7.02-7.23 (m, 6 H), 7.29-7.35 (m, 9H), 7.39 (d, J = 10.5 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H)	733 (MH+)
57i		(CDCl3) 3.42 (t, J = 6.6 Hz, 2 H), 4.58 (d, J = 5.8 Hz, 2 H), 4.81 (t, J = 6.6 Hz, 2 H), 5.16 (s, 2 H), 6.93-6.96 (m, 6 H), 7.11-7.44 (m, 20 H), 7.75-7.78 (m, 1 H), 8.19-8.22 (m, 1 H), 9.06 (t, J = 5.9 Hz, 1 H)	736 (MH+)
57j		(DMSO-d6) 3.57 (t, J = 7.0 Hz, 2 H), 4.57 (d, J = 5.9 Hz, 2 H), 4.94 (t, J = 7.0 Hz, 2 H), 5.56 (s, 2 H), 7.18-7.41 (m, 10 H), 7.61 (d, J = 7.6 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 8.09-8.12 (m, 1 H), 9.07 (t, J = 5.9 Hz, 1 H)	494 (MH+)
57k		(CDCl3) 2.74 (t, J = 6.8 Hz, 2 H), 3.21 (d, J = 7.4 Hz, 2 H), 4.07 (d, J = 6.8 Hz, 2 H), 4.79 (d, J = 7.4 Hz, 2 H), 5.28 (s, 2 H), 6.07-7.42 (m, 22 H), 7.79 (d, J = 8.2 Hz, 1 H)	656 (MH+)
57l	$CH_2OCH_2CH_2OCH_3$	(CDCl3) 3.30 (t, J = 6.9 Hz, 2 H), 3.31 (s, 3 H), 3.45-3.48 (m, 2 H), 3.64-3.67 (m, 2H), 4.82 (t, J = 6.9 Hz, 2 H), 5.27 (s, 2 H), 5.31 (s, 2 H), 6.94-6.97 (m, 6 H), 7.02-7.07 (m, 2 H), 7.14-7.23 (m, 4 H), 7.27-7.35 (m, 10 H), 7.78 (d, J = 7.8 Hz, 1 H)	691 (MH+)
57m	$CH_2CH_2CH_2CH_2CN$	(CD3OD) 3.34 (t, J = 6.9 Hz, 2 H), 4.80 (t, J = 6.9 Hz, 2 H), 5.03 (s, 2 H), 5.26 (s, 2 H), 6.73 (dd, J = 2.0, 6.5 Hz, 2 H), 6.97-7.01 (m, 1 H), 7.04-7.05 (m, 3 H), 7.20-7.31 (m, 4 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.55 (d, J = 7.1 Hz, 1 H)	467 (MH+)

5

Compound 58 (General Method)



The trityl protected tetrazole (75 mg, 0.12 mmol) compound was suspended in MeOH (5 mL) and to this solution was added conc. HCl (0.25 mL). The reaction was stirred for 1-2 hours at room temperature. The solvent was evaporated and the residue was dried under vacuum. The residue was then triturated with diethyl ether or methylene chloride to give the HCl salt .

The HCl salt was treated with exactly 2 eq 1N NaOH in methanol (one to remove the HCl and one to make the sodium salt of the tetrazole). The solvent was evaporated and the sodium salt was triturated with ether.

Method 2: The trityl protected tetrazole compound was treated with exactly 1 eq 1N NaOH in methanol. The reaction was heated at reflux and monitored by TLC and LC/MS for the completion of deprotection. The solvent was then evaporated and the residue was triturated with ether and/or methylene chloride to remove the trityl side product and filtration gave the final sodium salt product.

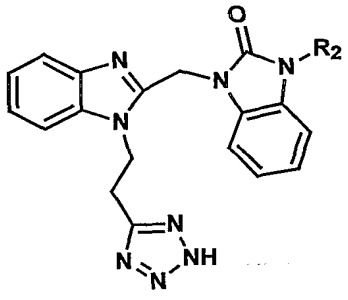
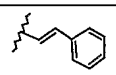
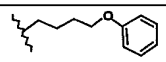
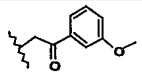
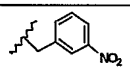
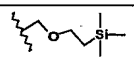
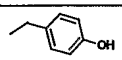
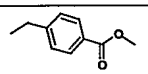
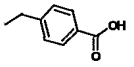
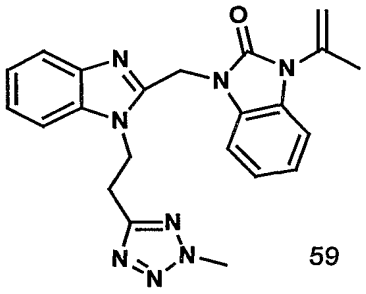


Table 10 – The trityl group was removed as described above for compound **58**.

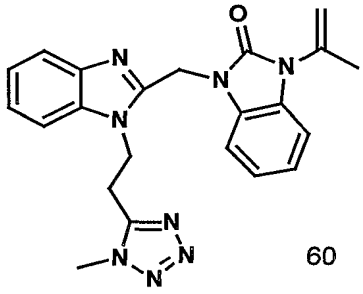
#	R_2	^{1}H-NMR Data	MS Data
58a	$CH_2CH_2CO_2Me$	(CD_3OD) δ 2.87 (t, J = 6.9Hz, 2H), 3.65 (s, 3H), 3.76 (t, J = 6.6Hz, 2H), 4.28 (t, J = 6.9 Hz, 2H), 5.17 (t, J = 6.6Hz, 2H), 5.89 (s, 2H), 7.18-7.29 (m, 2H), 7.38 (d, J = 8.7Hz, 2H), 7.61-7.73 (m, 3H), 7.97 (dd, J = 1.6, 6.9 Hz, 1H)	447 (MH+)
58b		(DMSO-d6) δ 3.27 (t under DMSO, 2 H), 4.66 (d, J = 5.0 Hz, 2 H), 4.87 (t, J = 6.9 Hz, 2 H), 5.45 (s, 2 H), 6.35-6.46 (m, 1 H), 6.60, 6.66 (s, 1 H), 7.03-7.08 (m, 2 H), 7.22-7.32 (m, 4 H), 7.40 (d, J = 7.0 Hz, 1 H), 7.55-7.60 (m, 1 H)	477 (MH+)
58c		(DMSO-d6) δ 1.69-1.87 (m, 4 H), 3.27 (t under DMSO, 2 H), 3.92-4.00 (m, 4 H), 4.89 (t, J = 6.9 Hz, 2 H), 5.51 (s, 2 H), 6.87-6.92 (m, 3 H), 7.01-7.12 (m, 2 H), 7.22-7.33 (m, 6 H), 7.59 (d, J = 7.4 Hz, 1 H), 7.66 (d, J = 8.2 Hz, 1 H)	509 (MH+)
58d		(DMSO-d6) δ 3.27 (t under DMSO, 2 H), 3.83 (s, 3 H), 4.86 (t, J = 6.9 Hz, 2 H), 5.49 (s, 2 H), 5.54 (s, 2 H), 7.02-7.05 (m, 2 H), 7.15-7.30 (m, 5 H), 7.49-7.61 (m, 4 H), 7.69 (d, J = 8.0 Hz, 1 H)	509 (MH+)
58e		(DMSO-d6) δ 3.27 (t under DMSO, 2 H), 4.92 (t, J = 7.1 Hz, 2 H), 5.27 (s, 2 H), 5.60 (s, 2 H), 7.04-7.07 (m, 2 H), 7.23-7.38 (m, 2 H), 7.60-7.71 (m, 3 H), 7.82 (d, J = 8.0 Hz, 1 H), 8.13-8.16 (m, 1 H), 8.26 (s, 1 H)	496 (MH+)
58f	CH_2OCH_3	(CD_3OD) δ 3.23 (s, 3 H), 3.37 (t, J = 6.9 Hz, 2 H), 4.80 (t, J = 6.9 Hz, 2 H), 5.22 (s, 2 H), 5.33 (s, 2 H), 6.99-7.03 (m, 1 H), 7.09-7.20 (m, 2 H), 7.22-7.32 (m, 3 H), 7.50-7.55 (m, 2 H)	405 (MH+)
58g		(DMSO-d6) δ 0.08 (s, 9 H), 0.85 (t, J = 8.0 Hz, 2 H), 3.14 (t, J = 6.6 Hz, 2 H), 3.56 (t, J = 8.1 Hz, 2 H), 4.67 (t, J = 6.6 Hz, 2 H), 5.18 (s, 2 H), 5.27 (s, 2 H), 6.98-7.13 (m, 4 H), 7.16-7.35 (m, 2H), 7.42 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H)	491 (MH+)
58h	CH_2CO_2Me	(DMSO-d6) δ 3.40 (t, J = 6.8 Hz, 2 H), 3.68 (s, 3 H), 4.79 (s, 2 H), 4.81 (t, J = 6.8 Hz, 2 H), 5.39 (s, 2 H), 7.04-7.07 (m, 2 H), 7.14-7.24 (m, 4 H), 7.50 (d, J = 7.9 Hz, 1 H), 7.56 (d, J = 7.6 Hz, 1 H)	433 (MH+)
58i	CH_2CO_2H	(DMSO-d6) δ 3.41 (t, J =7.2 Hz, 2 H), 4.65 (s, 2 H), 4.81 (t, J = 7.0 Hz, 2 H), 5.38 (s, 2 H), 7.01-7.08 (m, 2 H), 7.14-7.24 (m, 4 H), 7.49 (d, J = 7.5 Hz, 1 H), 7.56 (d, J = 7.4 Hz, 1 H)	419 (MH+)
58j		(CD_3OD) δ 3.34 (t, J = 6.9 Hz, 2 H), 4.80 (t, J = 6.9 Hz, 2 H), 5.03 (s, 2 H), 5.26 (s, 2 H), 6.73 (dd, J = 2.0, 6.5 Hz, 2 H), 6.97-7.01 (m, 1 H), 7.04-7.05 (m, 3 H), 7.20-7.31 (m, 4 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.55 (d, J = 7.1 Hz, 1 H)	467 (MH+)
58k		($CDCl_3$) δ 3.76 (t, J = 6.6 Hz, 2 H), 3.90 (s, 3 H), 5.18 (t, J = 6.6 Hz, 2 H), 5.27 (s, 2 H), 5.93 (s, 2 H), 7.17-7.23 (m, 3 H), 7.38-7.40 (m, 1H), 7.54 (d, J = 8.3 Hz, 2 H), 7.60-7.74 (m, 3 H), 7.96 (dd, J = 6.7, 1.6 Hz, 1 H), 8.02 (dd, J = 6.5, 1.8 Hz, 2 H)	509 (MH+)

581		(DMSO-d6) δ 3.45 (t, J = 7.0 Hz, 2 H), 4.84 (t, J = 7.0 Hz, 2 H), 5.17 (s, 2 H), 5.43 (s, 2 H), 6.98-7.05 (m, 2 H), 7.09-7.25 (m, 4H), 7.44 (d, J = 8.3 Hz, 2 H), 7.53 (t, J = 6.9 Hz, 2 H), 7.89 (d, J = 8.3 Hz, 2 H)	495 (MH+)

Compounds 59 and 60



59



60

To a solution of compound **52** (2.5 g, 6.24 mmol) and BTPP (2.92 g, 9.36 mmol) in THF (20 mL) was added iodomethane (1.06 g, 1.2 mmol). The reaction mixture was stirred for 3 hours at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography (gradient, EtOAc/hexanes, 2:1 to EtOAc/MeOH, 10:1) to give 2-methyl tetrazole product **59** (1.62 g, 63% yield) and 1-methyltetrazole product **60** (715 mg, 28% yield).

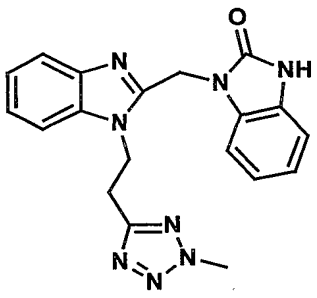
Compound 59

^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 3.26 (t, J = 7.3 Hz, 2H), 4.16 (s, 3H), 4.88 (t, J = 7.3 Hz, 2H), 5.25 (s, 1H), 7.38 (d, J = 1.3 Hz, 1H), 5.46 (s, 2H), 7.07-7.10 (m, 3H), 7.29-7.35 (m, 3H), 7.53-7.54 (m, 1H), 7.80-7.83 (m, 1H);
MS m/e 415 (MH^+);
Anal. Calcd for $C_{22}H_{22}N_8O$: C, 63.75; H, 5.35; N, 27.02
Found: C, 63.46; H, 5.61; N, 26.74.

Compound 60

^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 3.22 (t, J = 6.8 Hz, 2 H), 3.42 (s, 3 H), 4.89 (t, J = 6.8 Hz, 2 H), 5.31 (s, 1 H), 5.39 (d, J = 1.3 Hz, 1 H), 5.44 (s, 2 H), 7.06-7.13 (m, 3 H), 7.23-7.32 (m, 3 H), 7.55-7.61 (m, 1 H), 7.80 (d, J = 7.2 Hz, 1 H);
MS m/e 415 (MH^+).

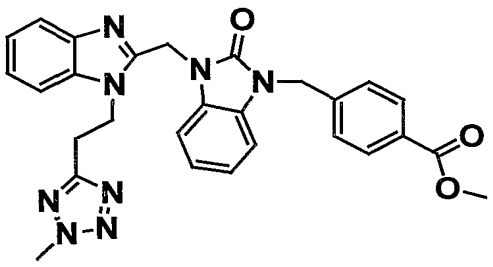
Compound 61



Compound **61** was prepared according to the same procedure as described for compound **6.**

^{1}H NMR (DMSO-d6) δ 3.34 (t over water, J = 6.9 Hz, 2H), 4.24 (s, 3H), 4.79 (t, J = 6.9 Hz, 2H), 5.23 (s, 2H), 6.91-7.00 (m, 3H), 7.09-7.23 (m, 3H), 7.48 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H);
MS m/e 375 (MH^+).

Compound 62



Compound **61** (1.00 g, 2.67 mmol) was suspended in THF / DMF (30 mL / 5 mL) and BTPP (1.67 g, 5.32 mmol) was added at room temperature. The solution was allowed to stir for 15-30 minutes at which time methyl 4-(bromomethyl)-benzoate (0.73 g, 3.20 mmol) was added. The reaction was stirred 16 hours at room temperature under nitrogen atmosphere. The solvent was removed and the resulting residue partitioned between water and EtOAc. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated. The crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate in hexanes to give compound **62.**

^{1}H NMR ($CDCl_3$) δ 3.24 (t, J = 7.3Hz, 2H), 3.90 (s, 3H), 4.17 (s, 3H), 4.88 (t, J = 7.3Hz, 2H), 5.17 (s, 2H), 5.54 (s, 2 H), 6.83 (dd, J = 7.7, 1.0 Hz, 1H), 6.99-7.10 (m, 2 H), 7.31-7.41 (m, 5H), 7.56 (d, J = 6.7 Hz, 1H), 7.82-7.85 (m, 1H), 7.99 (dd, J = 6.6, 1.8 Hz, 1H);

MS m/e 523 (MH^+).

Compound 63

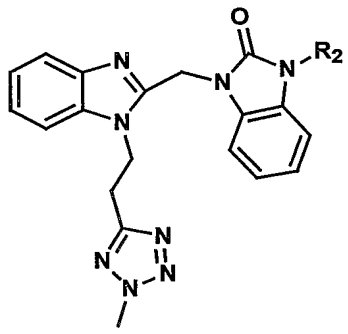
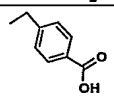
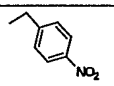
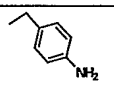
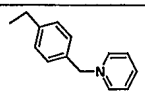
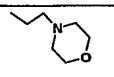
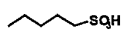
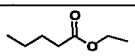
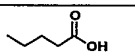
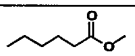
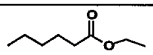
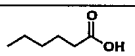
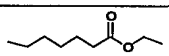
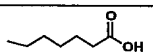
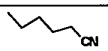
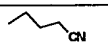
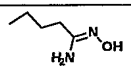
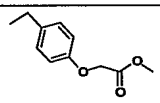
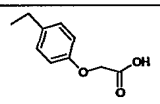


Table 11- Prepared as described for compound **62**.

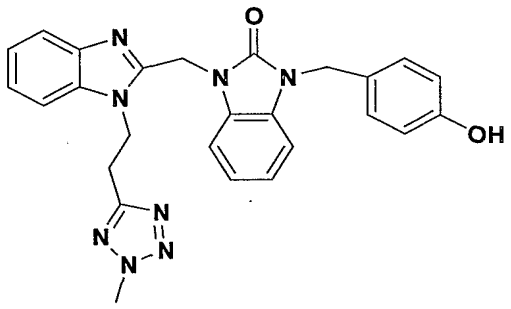
#	R_2	^{1}H-NMR Data	MS Data
63a[a]		(DMSO-d6) δ 3.36 (t, J = 6.8 Hz, 2 H), 4.25 (s, 3 H), 4.80 (t, J = 6.8 Hz, 2 H), 5.14 (s, 2 H), 5.36 (s, 2 H), 6.98-7.03 (m, 2 H), 7.09-7.23 (m, 4 H), 7.39 (d, J = 8.2 Hz, 2 H), 7.48-7.55 (m, 2 H), 7.86 (d, J = 8.2 Hz, 2 H)	509 (MH+)
63b		($CDCl_3$) δ 3.25 (t, J = 7.4 Hz, 2 H), 4.17 (s, 3 H), 4.90 (t, J = 7.4 Hz, 2 H), 5.21 (s, 2 H), 5.57 (s, 2 H), 6.84 (d, J = 7.5 Hz, 1 H), 7.05-7.14 (m, 2 H), 7.34-7.43 (m, 3 H), 7.50 (d, J = 8.9 Hz, 2 H), 7.64 (bd, J = 7.5 Hz, 1 H), 7.85-7.88 (m, 1 H), 8.19 (d, J = 8.9 Hz, 2 H)	510 (MH+)
63c[b]		(DMSO-d6) δ 3.50 (t, J = 6.7 Hz, 2 H), 424 (s, 3 H), 4.96 (t, J = 6.7 Hz, 2 H), 5.12 (s, 2 H), 5.61 (s, 2 H), 7.04-7.08 (m, 2 H), 7.15-7.19 (m, 1 H), 7.30-7.49 (m, 7 H), 7.69 (d, J = 7.1 Hz, 1 H), 7.83 (d, J = 7.7 Hz, 1 H)	480 (MH+)
63f[c]		(CD_3OD) δ 3.37 (t, J = 6.8 Hz, 2 H), 4.14 (s, 3 H), 4.87 (t, J = 6.9 Hz, 2 H), 5.20 (s, 2 H), 5.44 (s, 2 H), 5.84 (s, 2 H), 7.06-7.09 (m, 3 H), 7.18-7.21 (m, 1 H), 7.24-7.34 (m, 2 H), 7.46-7.53 (m, 5 H), 7.60 (dd, J = 1.6, 7.0 Hz, 1 H), 8.12 (t, J = 6.8 Hz, 2 H0, 8.62 (t, J = 7.9 Hz, 1 H), 9.06 (d, J = 5.8 Hz, 2 H)	556 (MH+)
63g		(CD_3OD) δ.68-3.74 (m, 4 H), 4.02 (bs, 4 H), 4.25 (s, 3 H), 4.49 (t, J = 5.7 Hz, 2 H), 5.13 (t, J = 6.5 Hz, 2 H), 5.78 (s, 2 H), 7.19-7.31 (m, 3 H), 7.42 (d, J = 7.4 Hz, 1 H), 7.61-7.70 (m, 2 H), 7.78 (dd, J = 2.4, 6.8 Hz, 1 H), 8.00 (d, J = 8.4 Hz, 1 H)	488 (MH+)
63h		(CD_3OD) δ 1.86-1.98 (m, 4 H), 2.89 (t, J = 7.3 Hz, 2 H), 3.32 (t, J = 7.0 Hz, 2 H), 4.01	511 (MH+)

		(t, J = 6.7 Hz, 2 H), 4.17 (s, 3 H), 4.85 (t, J = 7.0 Hz, 2 H), 5.41 (s, 2 H), 7.02-7.20 (m, 3 H), 7.25-7.33 (m, 3 H), 7.50 (dd, J = 2.0, 6.7 Hz, 1 H), 7.63 (dd, J = 2.0, 6.6 Hz, 1 H)	
63i		($CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3 H), 2.05-2.14 (m, 2 H), 2.41 (t, 7.3 Hz, 2 H), 3.18 (t, J = 7.6 Hz, 2 H), 3.98 (t, J = 8.7 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.81 (t, J = 7.3 Hz, 2 H), 5.42 (s, 2 H), 7.02-7.12 (m, 3 H), 7.23-7.34 (m, 3 H), 7.43-7.46 (m, 1 H), 7.77-7.80 (m, 1 H)	489 (MH+)
63j[a]		(DMSO-d6) δ 1.70-1.82 (m, 2 H), 1.89 (t, J = 7.6 Hz, 2 H), 3.31 (t, J = 6.9 Hz, 2 H), 3.83 (t, J = 7.3 Hz, 2 H), 4.25 (s, 3 H), 4.79 (t, J = 6.9 Hz, 2 H), 5.29 (s, 2 H), 6.97-7.07 (m, 2 H), 7.13-7.23 (m, 3 H), 7.33 (d, J = 7.2 Hz, 1 H), 7.52 (d, J = 7.3 Hz, 1 H), 7.55 (d, J = 7.4 Hz, 1 H)	460 (MH+)
63k		($CDCl_3$) δ 2.38 (t, J = 7.1 Hz, 2 H), 3.20 (t, J = 7.3 Hz, 2 H), 3.65 (s, 3 H), 3.93 (t, J = 6.9 Hz, 2 H), 4.18 (s, 3H), 4.83 (t, J = 7.4 Hz, 2 H), 5.45 (s, 2 H), 6.98-7.01 (m, 1 H), 7.05-7.09 (m, 2 H), 7.29-7.35 (m, 3 H), 7.48-7.50 (m, 1 H), 7.79-7.82 (m, 1 H)	489 (MH+)
63l		(DMSO-d6) δ 1.14 (t, J = 7.1 Hz, 3 H), 1.52-1.71 (m, 2 H), 2.34 (t, J = 7.4 Hz, 2 H), 3.12 (t over water, 2 H), 3.87 (t, J = 6.8 Hz, 2 H), 4.01 (q, J = 7.1 Hz, 2 H), 4.79 (t, J = 6.8 Hz, 2 H), 5.31 (s, 2 H), 6.99-7.09 (m, 2 H), 7.13-7.24 (m, 4 H), 7.49 (d, J = 7.5 Hz, 1 H), 7.54 (d, J = 7.6 Hz, 1 H)	
63m[a]		(DMSO-d6) δ 1.35-1.48 (m, 2 H), 1.56-1.64 (m, 2 H), 1.90 (t, J = 7.3 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 3.81 (t, J = 7.1 Hz, 2 H), 4.24 (s, 3 H), 4.78 (t, J = 6.8 Hz, 2 H), 5.29 (s, 2 H), 6.96-7.07 (m, 2 H), 7.11-7.22 (m, 4 H), 7.47 (d, J = 7.3 Hz, 1 H), 7.53 (d, J = 7.5 Hz, 1 H)	475 (MH+)
63n		($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3 H), 1.37-1.53 (m, 2 H), 1.62-1.93 (m, 4 H), 2.30 (t, J = 7.5 Hz, 2 H), 3.42 (t, J = 6.8 Hz, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 4.19 (s, 3 H), 4.81 (t, J = 7.2 Hz, 2 H), 5.42 (s, 2 H), 6.97 -7.12 (m, 3 H), 7.23-7.33 (m, 3 H), 7.43-7.46 (m, 1 H), 7.76-7.82 (m, 1 H)	517 (MH+)
63o[a]		(DMSO-d6) δ 1.20-1.30 (m, 2 H), 1.39-1.48 (m, 2 H), 1.50-1.66 (m, 2 H), 1.82 (t, J = 7.2 Hz, 2 H), 3.31 (t, J = 6.8 Hz, 2 H), 4.25 (s, 3 H), 4.79 (t, J = 7.0 Hz, 2 H), 5.30 (s, 2 H), 6.98-7.23 (m, 6 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.55 (d, J = 7.4 Hz, 1 H)	488 (MH+)
63p		($CDCl_3$) δ 2.94 (t, J = 7.0 Hz, 2 H), 3.16 (t, J = 6.9 Hz, 2 H), 4.16 (s, 3 H), 4.26 (t, J = 7.0 Hz, 2 H), 4.77 (t, J = 6.9 Hz, 2 H), 5.42 (s, 2 H), 7.06-7.17 (m, 3 H), 7.27-7.33 (m, 2 H), 7.35-7.39 (m, 1 H), 7.44-7.47 (m, 1 H), 7.78-7.83 (m, 1 H)	428 (MH+)
63q		(CD_3OD) δ 3.08 (s, 6 H), 3.68-3.72 (m, 4 H), 4.23 (s, 2 H), 4.45 (t, J= 5.7 Hz, 2 H), 5.11 (t, J = 6.5 Hz, 2 H), 5.74 (s, 2 H), 7.19-7.32 (m, 3 H), 7.41 (d, J = 7.4 Hz, 1 H), 7.58-7.68 (m, 2 H), 7.74 (d, J = 7.4 Hz, 1 H), 7.97 (d, J = 7.4 Hz, 1 H)	446 (MH+)

63r		($CDCl_3$) δ 1.70-1.80 (m, 2 H), 1.92-2.02 (m, 2 H), 2.46 (t, J = 7.0 Hz, 2 H), 3.20 (t, J = 7.4 Hz, 2 H), 3.98 (t, J = 6.7 Hz, 2 H), 4.18 (s, 3 H), 4.82 (t, J = 7.4 Hz, 2 H), 5.44 (s, 2 H), 6.98-7.07 (m, 1 H), 7.07-7.12 (m, 2 H), 7.28-7.37 (m, 3 H), 7.48-7.51 (m, 1 H), 7.78-7.84 (m, 1 H)	456 (MH+)
63s		($CDCl_3$) δ 2.10-2.24 (m, 2 H), 2.49 (t, J = 7.1 Hz, 2 H), 3.22 (t, J = 7.4 Hz, 2 H), 4.07 (t, J = 6.6 Hz, 2 H), 4.16 (s, 3 H), 4.87 (t, J = 7.4 Hz, 2 H), 5.51 (s, 2 H), 7.04-7.07 (m, 1 H), 7.11-7.15 (m, 2 H), 7.34-7.43 (m, 3 H), 7.56-7.64 (m, 1 H), 7.87-7.87 (m, 1 H)	442 (MH+)
63t[d]		(DMSO-d6) δ 1.82-1.93 (m, 2 H), 2.09 (t, J = 7.4 Hz, 2 H), 3.29-3.33 (m, 2 H), 3.85 (t, J = 6.9 Hz, 2 H), 4.24 (s, 3 H), 4.78 (t, J = 6.9 Hz, 2 H), 5.29 (s, 2 H), 6.16 (bs, 2 H), 6.99-7.08 (m, 2 H), 7.12-7.24 (m, 4 H), 7.48 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.4 Hz, 1 H), 9.09 (bs, 1 H)	475 (MH+)
63u		($CDCl_3$) δ 3.21 (t, J = 7.4 Hz, 2 H), 4.14 (s, 3 H), 4.84 (t, J = 7.4 Hz, 2 H), 5.12 (s, 2 H), 5.47 (s, 2 H), 6.87-6.92 (m, 1 H), 6.97-7.04 (m, 2 H), 7.24-7.35 (m, 8 H), 7.44-7.47 (m, 1 H), 7.77-7.83 (m, 1 H)	465 (MH+)
63v		(DMSO-d6) δ 3.36 (t, J = 6.7 Hz, 2 H), 3.66 (s, 3 H), 4.25 (s, 3H), 4.74 (s, 3H), 4.80 (t, J = 6.9 Hz, 2 H), 5.00 (s, 2 H), 5.33 (s, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.98-7.01 (m, 2 H), 7.13-7.23 (m, 4 H), 7.30 (d, J = 8.7 Hz, 2 H), 7.51 (dd, J = 7.7, 12.9 Hz, 2 H)	553 (MH+)
63w[a]		(DMSO-d6) δ 3.34 (t, J = 6.9 Hz, 2 H), 4.01 (s, 2 H), 4.27 (s, 3 H), 4.81 (t, J = 6.9 Hz, 2 H), 4.98 (s, 2 H), 5.34 (s, 2 H), 6.73 (d, J = 8.6 Hz, 2 H), 6.98-7.01 (m, 2 H), 7.13-7.25 (m, 6 H), 7.50 (d, J = 7.5 Hz, 1 H), 7.55 (d, J = 7.3 Hz, 1 H)	539 (MH+)

a, saponification of ester as described for compound **8**; **b**, catalytic hydrogenation as described for compound **123**; **c**, alkylation with 1,4-di(bromomethyl)benzene followed by addition of pyridine to form a pyridinium salt as described for **37g**; **d**, prepared as described for compound **119**.

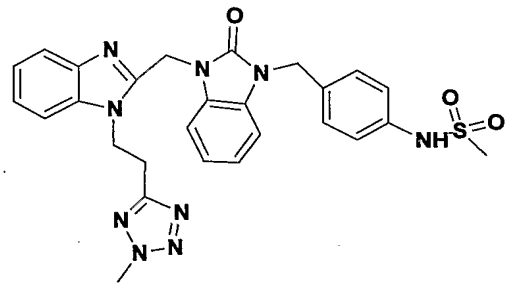
Compound 64



The general coupling method used for compound **63a** was applied using 4-benzyloxybenzyl chloride and BTPP in tetrahydrofuran to give the product benzyl ether. The benzyl ether (600 mg, 1.05 mmol) and 10% palladium hydroxide on carbon (160 mg) in 2:1 methanol/ tetrahydrofuran (50 mL / 25 mL) was agitated under hydrogen at 55 psi for 48 hours. The reaction mixture was filtered through a pad of Celite and then subjected to column chromatography (2:1 EtOAc/CH_2Cl_2) to give compound **64** as a white solid (262 mg, 52% yield).

^{1}H NMR (DMSO-d_6) δ 3.35 (t, J = 6.8 Hz, 2H), 4.25 (s, 3H), 4.80 (t, J = 6.8 Hz, 2H), 4.94 (s, 2H), 5.33 (s, 2H), 6.68 (d, J = 8.5 Hz, 2H), 6.95-7.02 (m, 2H), 7.09-7.23 (m, 6H), 7.47-7.54 (m, 2H), 9.39 (s, 1H);
IR (KBr, cm^{-1}) 3247, 2944, 1664, 1613, 1597, 1515, 1491, 1445, 1413, 747;
MS m/e 481 (MH^+);
Anal. Calcd for $C_{26}H_{24}N_8O_2$: C, 64.99; H, 5.03; N, 23.32
Found: C, 64.79; H, 4.98; N, 23.38.

Compound 65

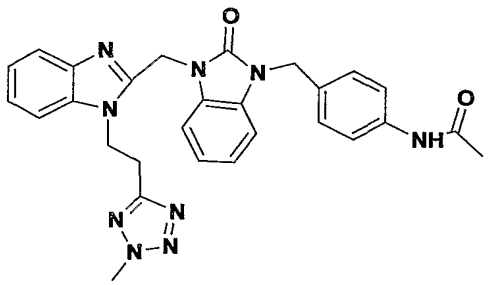


A mixture of compound **63c**, (100 mg, 0.18 mmol) and triethylamine (55 mg, 0.54 mmol) in methylene chloride (5 mL) was cooled to 0 °C. Methanesulfonyl chloride (21 mg, 0.18 mmol) was added and the reaction mixture was allowed to

warm gradually to room temperature. After stirring for 5.5 hours under nitrogen atmosphere, the organic material was washed with dilute aqueous sodium bicarbonate solution (10 mL). The aqueous layer was then extracted with methylene chloride (2 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated. Trituration with anhydrous diethyl ether followed by filtration gave compound **65** as a yellow solid (92 mg, 91% yield):

^{1}H NMR (CD_3OD) δ 2.95 (s, 3H), 3.07 (s, 1H), 3.68 (t, J = 6.5 Hz, 2H), 4.26 (s, 3 H), 5.14 (t, J = 6.7 Hz, 2H), 5.15 (s, 2H), 5.81 (s, 2H), 7.16-7.28 (m, 6H), 7.43 (d, J = 8.6 Hz, 2 H), 7.63-7.75 (m, 3H), 7.99-8.02 (m, 1H);
IR (KBr, cm^{-1}): 3435, 2929, 1708, 1615, 1513, 1493, 1404, 1329, 1152, 752.
MS m/e 558 (MH^+).

Compound 66

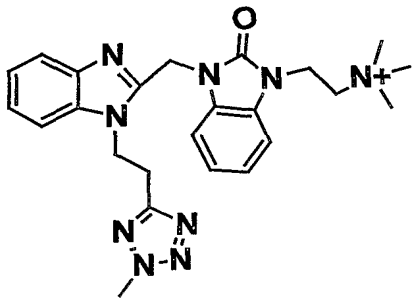


A mixture of compound **63c** (100 mg, 0.18 mmol) and triethylamine (55 mg, 0.54 mmol) in methylene chloride (4 mL) was cooled to 0 °C. Acetyl chloride (18 mg, 0.23 mmol) was added followed by DMAP (5 mg, catalytic quantity). The reaction mixture was allowed to warm to room temperature gradually and stirring was continued for 16 hours at room temperature under nitrogen atmosphere. A white precipitate was observed. The organic material was washed with dilute aqueous sodium bicarbonate solution (10 mL). The aqueous layer was then extracted with methylene chloride (2 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to give a white solid. The solid was triturated with anhydrous diethyl ether and filtered to give the compound **66** as a white solid (50 mg, 53 % yield).

^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3 H), 3.36 (t, J = 6.9 Hz, 2 H), 4.25 (s, 3 H), 4.80 (t, J = 6.9 Hz, 2 H), 5.14 (s, 2 H), 5.34 (s, 2 H), 6.97-7.02 (m, 2 H), 7.07-7.23 (m, 6 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.48-7.54 (m, 4 H), 9.92 (s, 1H).
IR (KBr, cm^{-1}): 3308, 2929, 1694, 1610, 1516, 1495, 1407, 1311, 749.
MS m/e 522 (MH^+).

Anal. Calcd for	$C_{28}H_{27}N_9O_2$:	C, 64.48; H, 5.22; N, 24.17
	Found:	C, 64.13; H, 5.32; N, 23.86

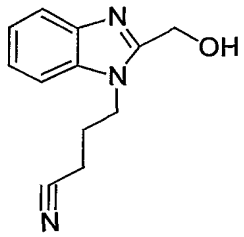
Compound 67



To a solution of compound **63q** (32 mg, 0.07 mmol) in acetone (1 mL) was added iodomethane (20 mg, 0.14 mmol). The reaction mixture was stirred at 50 °C for 2 hours and then stirred at room temperature overnight. The resulting precipitate was filtered and triturated with CH_2Cl_2 and Et_2O to give 18 mg (55% yield) of compound **67**.

^{1}H NMR (DMSO-d6) δ 3.19 (s, 9H), 3.51 (t, J = 7.0 Hz, 2H), 3.74 (t, J = 6.7 Hz, 2H), 4.39 (t, J = 6.7 Hz, 2H), 4.91 (t, J = 7.0 Hz, 2 H), 5.57 (bs, 2H), 7.08-7.19 (m, 2H), 7.27-7.28 (m, 3H), 7.41 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1 H), 7.73 (d, J = 7.7 Hz, 1H);
MS (m/e) 446 (MH^+).

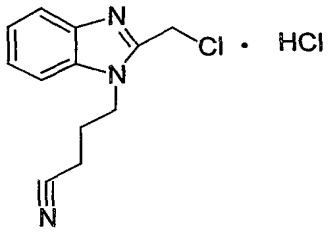
Compound 68



To a solution of 2-hydroxymethylbenzimidazole (29.63 g, 200 mmol) in a mixture of DMF/THF (150 mL, 1:1) was added sodium hydride (60% in mineral oil, 8.4 g, 210 mmol) in several portions at room temperature. After stirring for 1 hour, 4-bromobutyronitrile (29.6 g, 200 mmol) was added and the resulting solution was stirred at 80 °C for 16 hours. The solvent was evaporated and the residue diluted with water and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:1 to 2:1, then EtOAc/MeOH, 10:1) to give 22.11 g (51% yield) 4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyronitrile, **68** as a white solid.

^{1}H NMR ($CDCl_3$) δ 2.27-2.32 (m, 2H), 2.41 (t, J = 6.0 Hz, 2H), 4.41 (t, J = 7.2 Hz, 2H), 7.26-7.38 (m, 3H), 7.67-7.70 (m, 1H);
MS m/e 216 (MH^+).

Compound 69

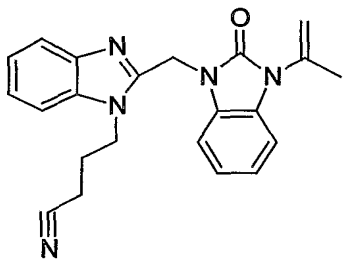


To 4-(2-hydroxymethyl-benzoimidazol-1-yl)-butyronitrile, **68**, (22 g, 102.2 mmol) suspended in CH_2Cl_2 (100 mL), thionyl chloride (15.81 g, 132.9 mmol) was slowly added with ice-water bath cooling. The ice bath was removed. The solution was stirred at room temperature for 1 hour and then evaporated. The residue was triturated with EtOAc to give a nearly quantitative yield of 4-(2-chloromethyl-benzoimidazol-1-yl)-butyronitrile, **69**, as light gray powder.

^{1}H NMR ($CDCl_3$) δ 2.32-2.38 (m, 2 H), 2.70 (t, J = 7.3 Hz, 2 H), 4.69 (t, J = 7.6 Hz, 2 H), 5.33 (s, 2 H), 7.69-7.74 (m, 2 H), 7.85-7.87 (m, 1 H), 8.00-8.02 (m, 1 H);
MS m/e 234 (MH^+).

Anal. Calcd for $C_{12}H_{12}N_3$•HCl•0.25 H_2O: C, 52.48; H, 4.95; N, 15.30
Found: C, 52.52; H, 4.88; N, 15.26

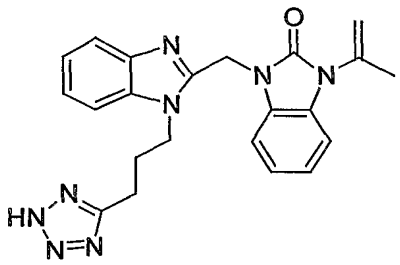
Compound 70



Compound **70** was prepared as described for **4**.

^{1}H NMR ($CDCl_3$) δ 1.93-2.06 (m, 2H), 2.29 (s, 3H), 7.65 (t, J = 7.6 Hz, 2H), 4.50 (t, J = 7.7 Hz, 2H), 5.22 (s, 1H), 5.40 (s, 2H), 5.42 (s, 1H), 7.10-7.17 (m, 3H), 7.30-7.38 (m, 3H), 7.53-7.57 (m, 1H), 7.79-7.83 (m, 1H);
MS m/e 372 (MH^+).

Compound 71



Compound **71** prepared as described for compound **52**.

^{1}H NMR (CD_3OD) δ 2.12-2.20 (m, 2H), 2.23 (s, 3H), 2.94 (t, J = 7.4 Hz, 2 H), 4.46 (t, J = 7.8 Hz, 2H), 4.92 (s, 2H), 5.23 (s, 1H), 5.45 (s, 2H), 7.05-7.33 (m, 6H), 7.45 (dd, J = 1.3, 6.8 Hz, 1H), 7.61 (dd, J = 1.7, 6.9 Hz, 1H);
MS m/e 415 (MH^+).

Compound 72

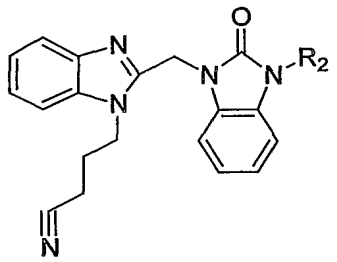
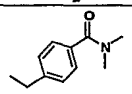
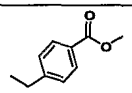
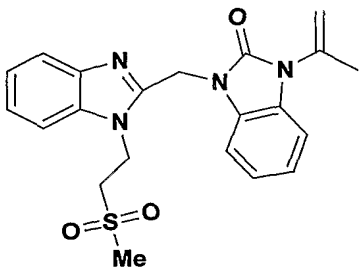


Table 12- Prepared by treatment of compound **71** as described for compound **6** followed by alkylation as described for compound **7** using Cs_2CO_3 instead of BTPP.

#	R_2	^{1}H-NMR Data	MS Data
72a		(DMSO-d6) 2.87 (s, 3 H), 2.96 (s, 3 H), 3.13 (t, J = 6.7 Hz, 2 H), 4.76 (t, J = 6.7 Hz, 2 H), 5.16 (s, 2 H), 5.50 (s, 2 H), 7.02-7.04 (m, 2 H), 7.16-7.21 (m, 2 H), 7.25-7.30 (m, 2 H), 7.37-7.42 (m, 4 H), 7.58 (d, J = 7.9 Hz, 1 H), 7.70 (d, J = 8.1 Hz, 1 H)	479 (MH+)
72b		(CDCl3) 2.74 (t, J = 6.7 Hz, 2 H), 3.92 (s, 3 H), 4.82 (t, J = 6.7 Hz, 2 H), 5.17 (s, 2 H), 5.51 (s, 2 H), 6.87 (d, J = 7.3 Hz, 1 H), 7.03-7.12 (m, 1 H), 7.33-7.43 (m, 6 H), 7.60 (d, J = 7.2 Hz, 1 H), 7.83-7.86 (m, 1 H), 8.02 (d, J = 8.3 Hz, 2 H)	466 (MH+)
72c		(DMSO-d6) δ 1.59-1.62 (m, 2 H), 1.76-1.79 (m, 2 H), 1.99-2.02 (m, 2 H), 2.54-2.63 (m, 4 H), 3.93 (t, *J* = 4.1, 2 H), 4.41 (t, *J* = 4.5, 2 H), 5.41 (s, 2 H), 6.99-7.19 (m, 4 H), 7.24-7.28 (m, 2 H), 7.56-7.60 (m, 2H);	413 (MH+)

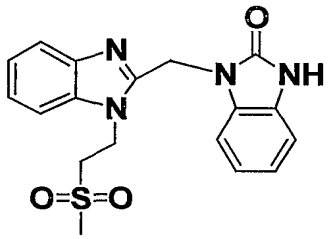
Compound 73



Compound **3** (2.00 g, 6.57 mmol) was suspended in acetonitrile (100 mL) and methyl vinyl sulfone (2.09 g, 19.72 mmol) was added followed by MTBD (50 mg, 0.33 mmol). The reaction mixture was heated at 50-60 °C for 16 hours. The solution became transparent. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (10:1 ethyl acetate/hexanes) to give 2.50g (93% yield) of compound **73** as a yellow-orange solid:

^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3 H), 3.07 (s, 3H), 3.39 (t, J = 7.6 Hz, 2H), 4.96 (t, J = 7.3 Hz, 2 H), 5.25 (s, 1 H), 5.42 (s, 1 H), 5.50 (s, 2H), 7.12-7.28 (m, 3H), 7.36-7.47 (m, 3H), 7.63 (d, J = 4.6 Hz, 1H), 7.83-7.86 (m, 1H);
IR (KBr, cm^{-1}) 1698, 1489, 1397, 1306, 1137, 745;
MS m/e 411 (MH^+).

Compound 74

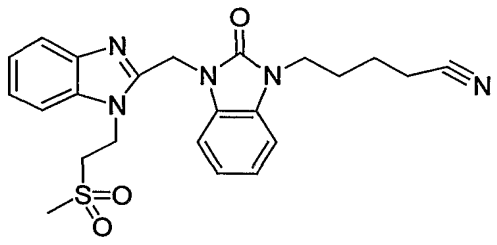


74

Compound **73** (2.2 g, 5.36 mmol) was suspended in MeOH (100 ml) and concentrated hydrochloric acid (10 mL). The mixture was heated at reflux for 3.5 hours and then stirred overnight at room temperature. The solvent was stripped, repeatedly evaporated with hexanes and/or diethyl ether, and dried under vacuum to give 2.2 g (quantitative yield) compound **74** as a hydrochloride salt:

^{1}H NMR (DMSO-d_6) δ 3.17 (s, 3H), 4.02 (t, J = 6.1 Hz, 2H), 5.24 (t, J = 6.1 Hz, 2H), 5.93 (s, 2H), 7.09-7.20 (m, 2H), 7.29 (bd, J = 8.0Hz, 1H), 7.65-7.73 (m, 2H), 8.06 (bd, J = 8.0 Hz, 1H);
IR (KBr, cm^{-1}) 1687, 1461, 1399, 1305, 1127, 751;
MS m/e 317 (MH^+).

Compound 75

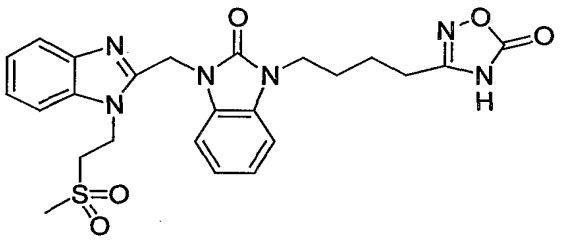


Compound **75** prepared as described for compound **7**.

^{1}H NMR ($CDCl_3$) δ 1.72-1.78 (m, 2H), 1.92-1.98 (m, 2H), 2.14-2.20 (m, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.85 (s, 3H), 3.07 (t, J = 7.6 Hz, 2H), 3.98 (t, J = 6.9 Hz, 2H), 4.54

(t, J = 7.7 Hz, 2H), 5.42 (s, 2H), 6.98-7.00 (m, 1H), 7.08-7.12 (m, 2H), 7.31-7.34 (m, 2H), 7.39-7.41 (m, 1H), 7.53-7.55 (m, 1H), 7.81 (dd, J = 3.1, 5.9 Hz, 1H);
MS (m/e) 466 (MH^+).

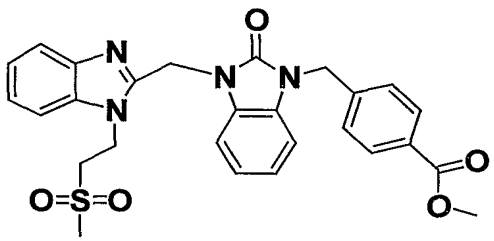
Compound 76



Compound **76** prepared as described for compound **121**.

^1H NMR (CD_3OD) δ 1.73-1.78 (m, 2H), 1.86-1.90 (m, 2 H), 2.15-2.19 (m, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.94 (s, 3H), 3.20 (t, J = 7.6 Hz, 2H), 4.03 (t, J = 6.9 Hz, 2H), 4.55 (t, J = 7.7 Hz, 2H), 5.47 (s, 2 H), 7.07 (t, J = 7.7 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.21-7.34 (m, 4H), 7.59 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H);
MS (m/e) 525 (MH^+).

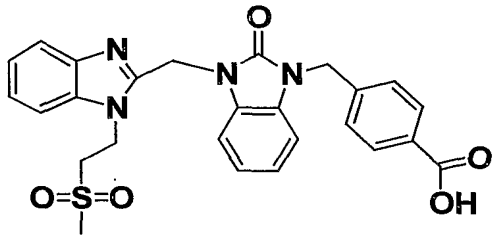
Compound 77



Compound **74** (2.20 g, 5.36 mmol) was suspended in anhydrous THF (70 mL). Upon addition of BTPP (6.70 g, 21.44 mmol), the reaction mixture became a clear solution. After stirring for 20 minutes, methyl 4-(bromomethyl)benzoate (1.47 g, 6.43 mmol) was added and the mixture was allowed to stir at room temperature under a nitrogen atmosphere for 16 hours. The solvent was evaporated. The brown residue was taken up in water (75 mL) and extracted with methylene chloride (3 x 300 mL). The organic extracts were dried over anhydrous $MgSO_4$, and evaporated. The product was purified by flash column chromatography (gradient with EtOAc/ hexanes 2:1 to 5:1 as eluantto give 1.2 g (43% yield) of compound **77**:

^{1}H NMR ($CDCl_3$) δ 2.99 (s, 3H), 3.43 (t, J = 7.3 Hz, 2H), 3.94 (s, 3H), 4.95 (t, J = 7.3 Hz, 2H), 5.17 (s, 2H), 5.55 (s, 2H), 6.86 (d, J = 7.7 Hz,1H), 7.03-7.15 (m, 2H), 7.36-7.7.47 (m, 4 H), 7.55 (d, J = 4.8 Hz, 1H), 7.65-7.86 (m, 1H), 8.02 (d, J = 8.1 Hz, 2H);
IR (KBr, cm^{-1}) 1707, 1493, 1438, 1408, 1282, 1135, 750;
MS m/e 519 (MH^+).

Compound 78

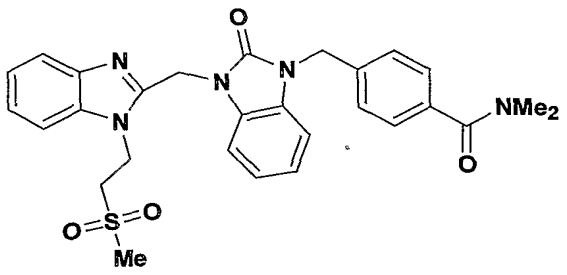


Ester **77** (1.2 g, 2.31 mmol) was suspended in a solution of methanol (75 mL) and 1 N NaOH (4.6 mL, 4.63 mmol). The reaction mixture was heated at reflux for 3 hours. The methanol was evaporated and the residue was taken up in water (75 mL). The aqueous solution was acidified to pH 6 with 1 N HCl. An unfilterable gelatinous precipitate came out of solution. A large amount of sodium chloride was added to the aqueous material to create a saturated solution which was then extracted with THF (400 mL x 3). The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to give 894 mg (81% yield) of compound **78** as a free acid.

The acid (500 mg, 0.99 mmol) was suspended in a mixture of methanol and THF (50%, 70 mL), and 1 N NaOH (0.99 mL, 0.99 mmol) was added. The solvent was evaporated and the solid was dried under vacuum. The solid was triturated with diethyl ether to give 464 mg (89% yield) of compound **78** as a sodium salt.

^{1}H NMR (DMSO-d_6) δ 3.10 (s, 3H), 3.78 (t, J = 6.5 Hz, 2H), 4.86 (t, J = 6.5 Hz, 2H), 5.09 (s, 2H), 5.52 (s, 2H), 6.97-7.29 (m, 8H), 7.57 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 8.1 Hz, 2H);
IR (KBr, cm^{-1}) 3398, 2926, 1698, 1597, 1554, 1493, 1392, 1293, 1132, 750;
MS m/e 505 (MH^+).

Compound 79

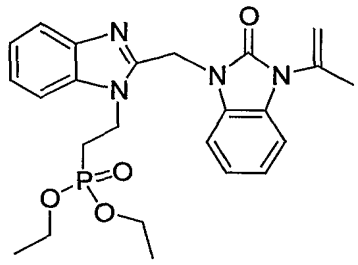


Acid **78** (400 mg, 0.79 mmol), dimethylamine hydrochloric acid salt (97 mg, 1.19 mmol), and N,N-diisopropylethylamine (307 mg, 2.38 mmol) were stirred in DMF (10 mL). To this solution was added PyBroP (433 mg, 0.95 mmol). The reaction was allowed to stir under nitrogen atmosphere at room temperature for 48 hours. The solvent was evaporated. The residue was taken up in water (20 mL) and extracted with ethyl acetate (3 x 150 mL). The organic extracts were dried over anhydrous $MgSO_4$, and evaporated. Column chromatography (methylene chloride /methanol = 20:1) followed by preparative high pressure liquid chromatography (reverse phase) gave 110 mg (26% yield) of compound **79**:

^1H NMR (CD_3OD) δ 2.96, 3.05, 3.08 (s, 3H each), 3.83(t, J =3.8 Hz, 2H), 5.07 (t, J = 3.8 Hz, 2H), 5.21 (s, 2H), 5.77 (s, 2H), 7.08 (bs, 3H), 7.28-7.30 (m, 1 H), 7.41 (d, J = 4.9 Hz, 2H), 7.44-7.53 (m, 4H), 7.65 (d, J = 4.9 Hz, 1H), 7.79 (d, J = 4.9 Hz, 1H);
IR (KBr, cm^{-1}) 3441, 1702, 1621, 1493, 1406, 1133, 750;
MS m/e 532 (MH^+);

Anal. Calcd for $C_{28}H_{29}N_5O_4S \bullet 2H_2O$: C, 59.24; H, 5.86; N, 12.34
Found: C, 59.00; H, 5.15; N, 12.17.

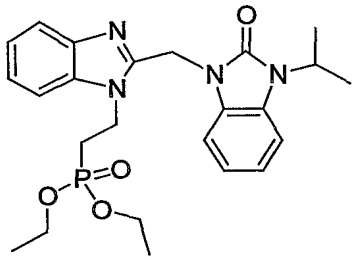
Compound 80



Compound **80** was prepared as described for **50** except ethyl vinylphosphinate was used in place of acrylonitrile.

^{1}H NMR (DMSO-d6) δ 1.10 (t, J = 7.1, 6H), 2.11 (s, 3H), 2.29-2.40 (m, 2H), 3.85-3.95 (m, 4H), 4.54-4.64 (m, 2H), 5.20 (s, 1H), 5.40 (s, 1H), 5.45 (s, 2H), 7.02-7.09 (m, 2 H), 7.14-7.32 (m, 4H), 7.50-7.57 (m, 2H);
MS (m/e) 469 (MH^+).

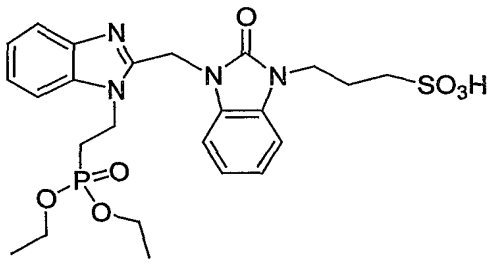
Compound 81



The isopropenyl group of compound **80** was reduced to give compound **81** as described for compound **54**.

^{1}H NMR (DMSO-d6) δ 1.10 (t, J = 7.0, 6H), 1.46 (d, J = 7.0, 6H), 2.24-2.35 (m, 2H), 3.85-3.95 (m, 4H), 4.53-4.70 (m, 3H), 5.41 (s, 2H), 6.96-7.06 (m, 2H), 7.14-7.34 (m, 4H), 7.48-7.57 (m, 2H);
MS (m/e) 471 (MH^+).

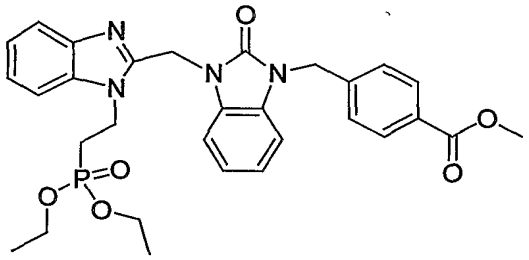
Compound 82



Compound **82** was prepared as described for compound **7** using [1,2]oxathiolane 2,2-dioxide as the alkylating agent.

^{1}H NMR (DMSO-d6) δ 1.10 (t, J = 7.0, 6H), 1.90-2.0 (m, 2H), 2.28-2.47 (m, 4H), 3.85-3.98 (m, 6H), 4.52-5.62 (m, 2H), 5.44 (s, 2 H), 6.96-7.08 (m, 2H), 7.12-7.29 (m, 4H), 7.48-7.57 (m, 2H);
MS (m/e) 551 (MH^+).

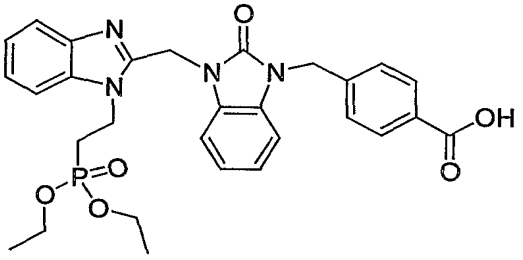
Compound 83



Compound **83** was prepared as described for compound **7**.

^{1}H NMR (DMSO-d6) δ 1.09 (t, J = 7.1, 6H), 2.32-2.43 (m, 2H), 3.82 (s, 3H), 3.84-3.94 (m, 4H), 4.55-4.64 (m, 2H), 5.20 (s, 2H), 5.51 (s, 2H), 6.97-7.04 (m, 2H), 7.09-7.31 (m, 4H), 7.46-7.56 (m, 4H), 7.93 (d, J = 8.3, 2H);
MS (m/e) 577 (MH^+).

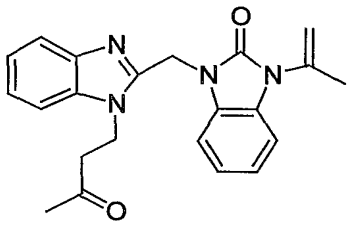
Compound 84



Compound **84** was prepared as described for compound 4.

^{1}H NMR (DMSO-d6) δ 1.09 (t, J = 7.1, 6H), 7.38-2.44 (m, 2H), 3.86-3.95 (m, 4H), 4.61-4.69 (m, 2H), 5.20 (s, 2H), 5.62 (s, 2H), 7.01-7.04 (m, 2H), 7.25-7.37 (m, 2H), 7.46 (d, J = 8.2, 2H), 7.59-7.66 (m, 2H), 7.90 (s, 2H);
MS (m/e) 563 (MH^+).

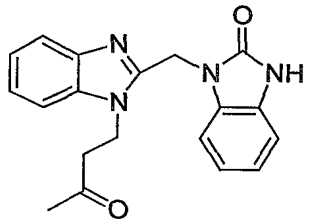
Compound 85



Compound **85** was prepared as described for **50** using methyl vinyl ketone.

^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.45 (s, 3H), 2.84 (t, J = 6.8 Hz, 2H), 4.64 (t, J = 6.8 Hz, 2H), 5.21 (s, 1H), 5.38 (d, J = 1.3 Hz, 1H), 5.51 (s, 2H), 7.06-7.10 (m, 3H), 7.28-7.31 (m, 2H), 7.34-7.38 (m, 1H), 7.49-7.52 (m, 1H), 7.77-7.80 (m, 1H);
MS m/e 375 (MH^+).

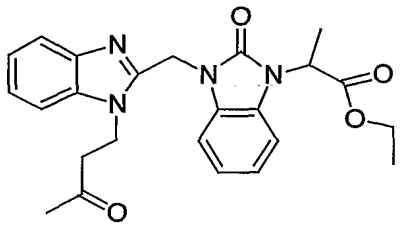
Compound 86



Compound **86** was prepared as described for compound **6**.

^{1}H NMR ($CDCl_3$) 2.09 (s, 3H), 2.82 (t, J = 6.8 Hz, 2H), 3.50 (s, 1H), 4.63 (t, J = 6.9 Hz, 2H), 5.51 (s, 2H), 7.04-7.07 (m, 3H), 7.29-7.37 (m, 2H), 7.44-7.45 (m, 1H), 7.78-7.81 (m, 1H), 8.64 (s, 1H);
MS m/e 335 (MH^+).

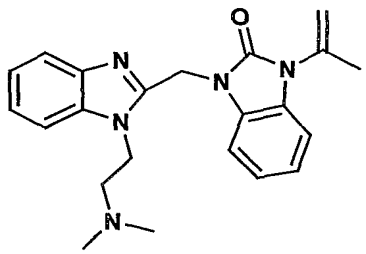
Compound 87



Compound **87** was prepared as described for compound **7** using 2-bromo-propionic acid ethyl ester.

^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.1 Hz, 3H), 1.57 (d, J = 7.4 Hz, 3H), 2.08 (s, 3H), 2.77 (t, J = 6.9 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.60 (t, J = 6.9 Hz, 2H), 5.27 (q, J = 7.4 Hz, 1H), 5.51 (q, J = 12.4 Hz, 2H), 6.93-6.96 (m, 1H), 7.09-7.09 (m, 2H), 7.28-7.32 (m, 2H), 7.34-7.38 (m, 1 H), 7.48-7.51 (m, 1H), 7.77-7.81 (m, 1H);
MS m/e 435 (MH^+).

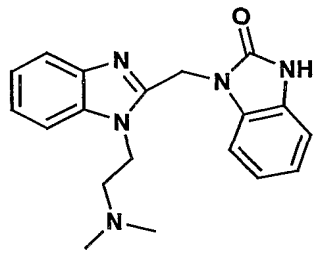
Compound 88



To compound **3** (1.62 g, 5.32 mmol) in anhydrous DMF (20 mL) was added NaH (60% in mineral oil, 510 mg, 12.77 mmol), followed by 2-chloroethyl dimethylamine hydrochloride (843 mg, 5.85 mmol). The mixture was stirred at 65°C overnight. The solution was poured into saturated sodium bicarbonate and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, and evaporated The residue was purified by chromatography (EtOAc:MeOH, 10:1) to give 1.72g (86% yield) of compound **88** as a solid:

^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 2.25 (s, 6H), 2.48 (t, J = 6.7 Hz, 2H), 4.45 (t, J = 6.7 Hz, 2H), 5.21 (s, 1H), 5.37 (s, 1H), 5.39 (s, 2H), 7.03-7.09 (m, 3H), 7.24-7.34 (m, 3H), 7.49-7.52 (m, 1H), 7.75-7.79 (m, 1H);
IR (KBr, cm^{-1}) 2941, 2830, 2774, 1693, 1396, 1157, 747, 732;
MS m/e 376 (MH^+);
Anal. Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65
Found: C, 70.29; H, 6.78; N, 18.76.

Compound 89

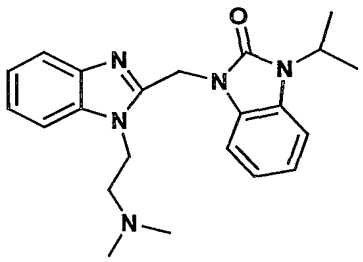


89

Compound **89** was prepared as described for compound **6**.

^{1}H NMR ($CDCl_3$) δ 2.29 (s, 6H), 2.50 (t, J = 7.2Hz, 2H), 4.45 (t, J = 7.2Hz, 2H), 5.40 (s, 2H), 7.00-7.05 (m, 3H), 7.27-7.30 (m, 2H), 7.35-7.37 (m, 1H), 7.42-7.44 (m, 1H), 7.77-7.80 (m, 1H), 8.41 (bs, 1H);
MS m/e 336 (MH^+).

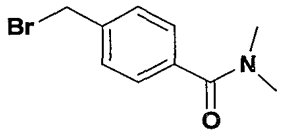
Compound 90



The isopropenyl group of compound **88** was reduced to the isopropyl group as described for compound **115**.

^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 7.0 Hz, 6H), 2.27 (s, 6H), 2.47 (t, J = 6.8Hz, 2H), 4.44 (t, J = 6.8Hz, 2H), 4.72-4.82 (m, 1H), 5.39 (s, 2H), 6.98-7.06 (m, 2H), 7.07-7.13 (m, 1H), 7.24-7.33 (m, 3H), 7.48-7.52 (m, 1H), 7.75-7.79 (m, 1H);
MS m/e 413 (MH^+).

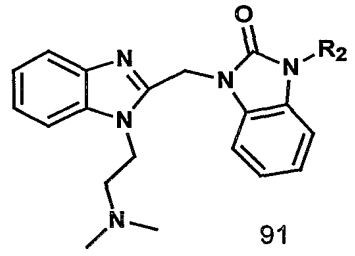
4-Bromomethyl-N,N-dimethyl-benzamide



4-bromomethylbenzoic acid (25 g, 116.25 mmol) was dissolved in CH_2Cl_2 (200 ml) and treated with oxalyl chloride (12.2 ml, 139.5 mmol). DMF (0.45 ml) was added slowly then stirred for 1 h. The solvent was removed to give the 4-bromomethylbenzoyl chloride as a white solid.

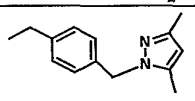
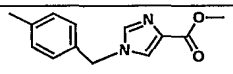
A mixture of 4-bromomethyl-benzoyl chloride (7.0 g, 30.24 mmol), polyvinyl pyridine (9.6 g , 90.7 mmol) and dimethyl amine (15.9 ml, 31.8 mmol, 2.0 M in THF) was stirred at 23°C for 15 h. The solution was filtered and the solvent removed to give 7.3 g (99% yield) of 4-bromomethyl-N,N-dimethyl-benzamide as a yellow solid.

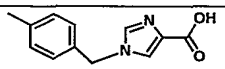
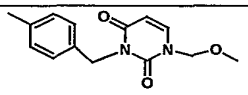
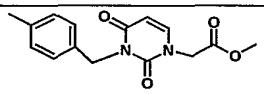
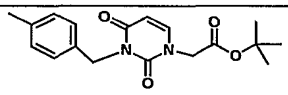
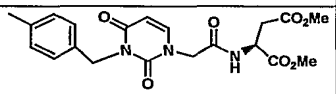
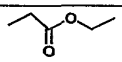
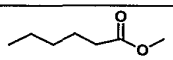
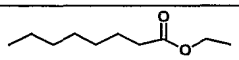
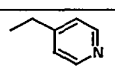
^{1}H NMR ($CDCl_3$) δ 2.98 (s, 3H), 3.10 (s, 3H), 4.49 (s, 2H), 7.37-7.43 (m, 4H).
MS m/e 242 (MH^+).

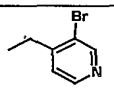
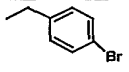
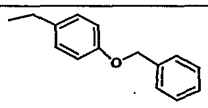
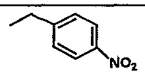
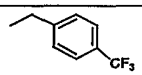
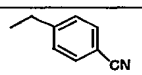
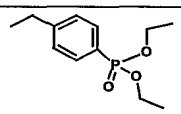
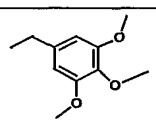


91

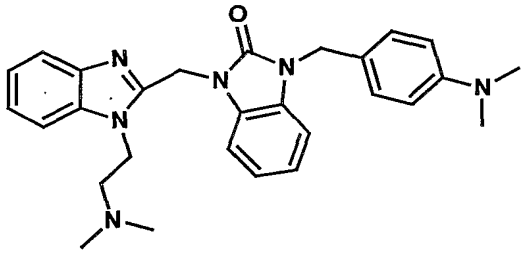
Table 13- Compounds in the table below were prepared by alkylation of compound **89** as described for compound **7**.

#	R_2	^{1}H-NMR Data	MS Data
91a		(CD_3OD) 2.36 (s, 3H), 2.39 (s, 3H), 3.10 (s, 6H), 3.87 (t, J = 7.9Hz, 2H), 5.19 (t, J = 7.9Hz, 2H), 5.19 s, 2H), 5.46 (s, 2H), 5.90 (s, 2H), 6.37 (s, 1H), 7.16-7.23 (m, 5H), 7.45 (d, J = 8.2Hz, 3H), 7.68-7.79 (m, 3H), 8.12 (d, J = 8.5Hz, 1H)	534 (MH+)
91b		(CD_3OD) δ 3.12 (s, 6 H), 3.85 (t, J = 7.4 Hz, 2 H), 3.91 (s, 3 H), 5.17-5.24 (m, 2 H), 5.21 (s, 2 H), 5.78 (s, 2 H), 5.90 (s, 2 H), 7.06-7.25 (m, 3 H), 7.38 (d, J = 7.9 Hz, 2 H), 7.46 (d, J = 8.3 Hz, 3 H), 7.65-7.79 (m, 3 H), 8.10 (d, J = 8.3 Hz, 1 H), 8.31 (s, 1 H), 9.23 (s, 1 H)	564 (MH+)

91c		(DMSO-d6) δ 2.21 (s, 6 H), 2.56 (t, J = 6.5 Hz, 2 H), 4.39 (t, J = 6.4 Hz, 2 H), 5.08 (s, 2 H), 5.43 (s, 2 H), 5.51 (s, 2 H), 6.98-6.99 (m, 2 H), 7.10 (d, J = 8.1 Hz, 2 H), 7.14-7.25 (m, 4 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.54-7.56 (m, 4 H), 8.00 (bs, 1 H)	550 (MH+)
91d		($CDCl_3$) 2.30 (s, 6H), 2.52-2.63 (m, 2H), 3.38 (s, 3H), 4.47-4.59 (m, 2H), 5.08 (s, 2H), 5.10 (s, 4H), 5.45 (s, 2H), 5.81 (d, J = 7.9Hz, 1H), 6.87-6.90 (m, 1H), 7.00-7.04 (m, 2H), 7.23-7.30 (m, 5H), 7.42 (d, J = 8.0 Hz, 3H), 7.49-7.52 (m, 1H), 7.78-7.81 (m, 1H)	594 (MH+)
91e		(CD_3OD) 3.03 (s, 6H), 3.73 (s, 3H), 3.74-3.80 (m, 2H), 4.56 (s, 2H), 5.07 (s, 2H), 5.12 (s, 2H), 5.12-5.20 (m, 2H), 5.76 (d, J = 7.5Hz, 1H), 5.87 (s, 2H), 7.17-7.20 (m, 3H), 7.28-7.33 (m, 4H), 7.44-7.46 (m, 1H), 7.54 (d, J = 7.8Hz, 1H), 7.63-7.78 (m, 3H), 8.11 (d, J = 8.1Hz, 1H)	622 (MH+)
91f		(DMSO-d6) 1.33 (s, 9H), 2.88 (s, 3H), 2.89 (s, 3H), 3.67-3.41 (m, 2H), 4.44 (s, 2H), 4.94 (s, 2H), 4.96-5.01 (m, 2H), 5.09 (s, 2H), 5.68 (s, 2H), 5.78 (d, J = 7.9Hz, 1H), 7.04-7.07 (m, 2H), 7.16-7.19 (m, 1H), 7.21 (d, J = 8.2Hz, 2H), 7.32 (d, J = 8.2Hz, 2H), 7.39-7.47 (m, 3H), 7.69 (t, J = 8.3Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H)	664 (MH+)
91g		($CDCl_3$) 2.26 (s, 6H), 2.52 (t, J = 6.9Hz, 2H), 2.82 (dd, J = 4.5, 17.4Hz, 1H), 3.00 (dd, J = 4.5, 17.1Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 4.37 (d, J = 5.1Hz, 2H), 4.47 (t, J = 7.1Hz, 2H), 4.80-4.84 (m, 1H), 5.04 (s, 4H), 5.44 (s, 2H), 5.76 (d, J = 7.8Hz, 1H), 6.85-6.88 (m, 1H), 6.97-7.00 (m, 2H), 7.14 (d, J = 8.1Hz, 1H), 7.19-7.29 (m, 4H), 7.35-7.47 (m, 4H), 7.75-7.78 (m, 1H)	751 (MH+)
91h		(DMSO-d6) δ 1.22 (t, J = 7.1Hz, 3H), 2.36 (s, 6H), 2.71-2.82 (s, 2H), 4.16 (q, J = 7.1Hz, 2H), 4.52 (t, J = 6.4Hz, 2H), 4.79 (s, 2H), 5.43 (s, 2H), 7.00-7.10 (m, 2H), 7.10-7.30 (m, 4H), 7.61-7.72 (m, 2H)	421 (MH+)
91i		(CD_3OD) 1.66-1.72 (m, 2H), 1.83-1.88 (m, 2H), 2.41 (t, J = 7.2Hz, 2H), 3.14 (s, 6H), 3.62 (s, 3H), 3.87 (t, J = 8.0 Hz, 2H), 4.02 (t, J = 6.8Hz, 2H), 5.19 (t, J = 7.8Hz, 2H), 5.86 (s, 2H), 7.22-7.34 (m, 3H), 7.45-7.48 (m, 1H), 7.67-7.79 (m, 3H), 8.11 (d, J = 8.0 Hz, 1H)	450 (MH+)
91j		(CDCl3) 1.21-1.29 (m, 3 H), 1.36-1.46 (m, 2 H), 1.64-1.84 (m, 6 H), 2.29-2.33 (m, 6 H), 2.52 (m, 2 H), 3.88-3.93 (m, 2 H), 4.07-4.14 (m, 2 H), 4.43-4.48 (m, 2 H), 5.42 (s, 2 H), 6.91-7.50 (m, 6 H), 7.75-7.81 (m, 2 H)	478 (MH+)
91k		(CD_3OD) 3.11 (s, 6 H), 3.77 (t, J = 7.8 Hz, 2 H), 5.05 (t, J = 7.8 Hz, 2 H), 5.53 (s, 2 H), 5.72 (s, 2 H), 7.13-7.25 (m, 3 H), 7.72 (d, J = 7.8 Hz, 1 H),	427 (MH+)

		7.85 (d, J = 8.1 Hz, 1 H), 8.03-8.06 (m, 2 H), 8.83 (bs, 2 H)	
91l		(CD_3OD) 3.11 (s, 6 H), 3.77 (t, J = 7.9 Hz, 2 H), 5.02 (t, J = 7.9 Hz, 2 H), 5.52 (s, 2 H), 5.68 (s, 2 H), 7.07 (d, J = 8.4 Hz, 1 H), 7.32 (dd, J = 1.6, 8.4 Hz, 1 H), 7.43-7.55 (m, 2 H), 7.70-7.73 (m, 2 H), 7.83 (d, J = 7.9 Hz, 1 H), 8.03 (d, J = 6.3 Hz, 2 H), 8.83 (d, J = 6.0 Hz, 2 H)	505,507 (MH+)
91m		(CD_3OD) 3.09 (s, 6 H), 3.82-3.95 (m, 2 H), 5.13 (s, 2 H), 5.20-5.24 (m, 2 H), 5.94 (s, 2 H), 7.17-7.24 (m, 3 H), 7.30-7.38 (m, 2 H), 7.47-7.52 (m, 3 H), 7.65-7.78 (m, 3 H), 8.18 (d, J = 8.0 Hz, 1 H)	506 (MH+)
91n		($CDCl_3$) 2.31 (s, 6 H), 2.57 (t, J = 6.6 Hz, 2 H), 4.53 (t, J = 6.7 Hz, 2 H), 5.04 (s, 2 H), 5.06 (s, 2 H), 5.46 (s, 2 H), 6.92-6.95 (m, 3 H), 7.01-7.04 (m, 2 H), 7.27-7.43 (m, 10 H), 7.49-7.52 (m, 1 H), 7.79-7.83 (m, 1 H)	532 (MH+)
91o		(CD_3OD) 3.13 (s, 6 H), 3.87 (t, J = 7.9 Hz, 2 H), 5.20 (t, J = 7.7 Hz, 2 H), 5.34 (s, 2 H), 5.91 (s, 2 H), 7.19-7.24 (m, 3 H), 7.48-7.52 (m, 1 H), 7.63-7.77 (m, 5 H), 8.09-8.12 (m, 1 H), 8.22-8.26 (m, 2 H)	505 (M-H-)
91p		(CD_3OD) 3.12 (s, 6 H), 3.89 (t, J = 7.9 Hz, 2 H), 5.24 (t, J = 7.9 Hz, 2 H), 5.29 (s, 2 H), 5.96 (s, 2 H), 7.19-7.24 (m, 3 H), 7.50-7.53 (m, 1 H), 7.60 (d, J = 8.3 Hz, 1 H), 7.67 (d, J = 7.5 Hz, 1 H), 7.71-7.80 (m, 5 H), 8.17 (d, J = 8.1 Hz, 1 H)	494 (MH+)
91q		(CD_3OD) 2.02-2.33 (m, 4 H), 3.22-3.33 (m, 2 H), 3.78-3.89 (m, 2 H), 3.90 (s, 3 H), 3.94 (t, J = 7.9 Hz, 2 H), 5.21 (t, J = 7.2 Hz, 2 H), 5.27 (s, 2 H), 5.94 (s, 2 H), 7.17- 7.25 (m, 3 H), 7.49-7.53 (m, 3 H), 7.69-7.81 (m, 3 H), 8.02 (d, J = 8.2 Hz, 2 H), 8.16 (d, J = 7.9 Hz, 1 H)	510 (MH+)
91r		(DMSO-d6) 1.27 (t, J = 6.9 Hz, 6 H), 3.29 (s, 6 H), 3.81 (t, J = 7.6 Hz, 2 H), 4.06-4.12 (m, 4 H), 5.19 (t, J = 7.6 Hz, 2 H), 5.26 (s, 2 H), 5.88 (s, 2 H), 7.16-7.21 (m, 3 H), 7.46-7.79 (m, 8 H), 8.09 (d, J = 7.8 Hz, 1 H)	562 (MH+)
91s		($CDCl_3$) 2.79 (s, 6 H), 3.41-3.69 (m, 2 H), 3.52 (s, 3 H), 3.62 (s, 6 H), 4.82 (bs, 2 H), 5.22-5.36 (m, 2 H), 5.77 (bs, 2 H), 6.32 (s, 2 H), 6.77 (d, J = 7.8 Hz, 1 H), 6.85-7.03 (m, 2 H), 7.18-7.29 (m, 1 H), 7.35-7.51 (m, 2 H), 7.82-7.92 (m, 1 H), 8.10-8.25 (m, 1 H)	516 (MH+)

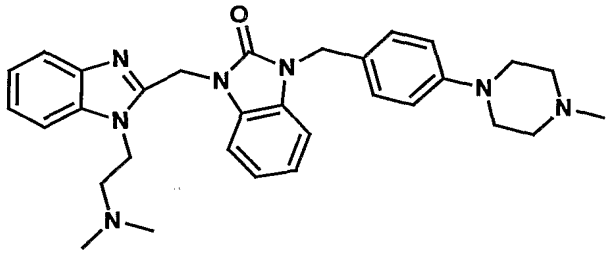
Compound 92



To a solution of compound **89** (502 mg, 1.5 mmol), 4-N,N-dimethylaminobenzyl alcohol (prepared as described by Swami, S. S. et al, Synth Commun., 29(12), 2129-2131, 1999) (272 mg, 1.8 mmol), and 1,1'-(azodicarbonyl)dipiperidine (453 mg, 1.8 mmol) in THF was added tributylphosphine (364 mg, 1.8 mmol) at 0°C. The final solution was allowed to warm to room temperature and stirred for 12 h. The solvent is evaporated the and the residue purified by preparative reverse phase HPLC to yield 420 mg (60%) of compound **92** as a viscous oil.

^{1}H NMR (DMSO-d6) δ 3.06 (s, 6H), 3.16 (s, 6H), 3.67 (t, J = 7.5 Hz, 2H), 4.99 (t, J = 7.5 Hz, 2H), 5.18 (s, 2H), 5.61 (s, 2H), 7.09-7.18 (m, 3H), 7.37-7.53 (m, 7H), 7.66-7.78 (m, 2H);
MS m/e 469 (MH^+).

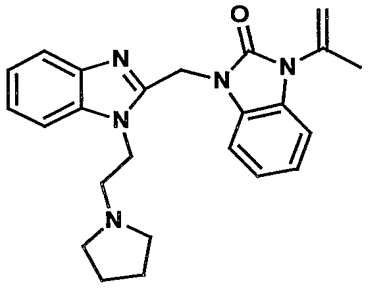
Compound 93



A mixture of compound **91i** (50 mg, 0.10 mmol), N-methylpiperidine (12 mg, 0.12 mmol), sodium t-butoxide (14 mg, 0.15 mmol), dipalladium (0) (9 mg, 0.01 mmol) and (R)-(+)-BINAP (19 mg, 0.03 mmol) in toluene (2 ml) was heated to 100°C for 2 h. The solvent is evaporated and the residue purified by preparative reverse phase-HPLC to yield 54 mg (100%) of compound **93** as a white solid.

^{1}H NMR (CD_3OD) δ 2.93 (s, 3H), 3.05 (s, 6H), 3.18-3.24 (m, 2H), 3.57-3.69 (m, 4H), 3.78-3.82 (m, 2H), 4.92-4.98 (m, 2H), 5.09 (s, 2 H), 5.56 (s, 2H), 6.98-6.99 (m, 2H), 7.06-7.09 (m, 3 H), 7.28-7.34 (m, 2H), 7.38-7.47 (m, 3H), 7.66-7.72 (m, 2H);
MS m/e 524 (MH+).

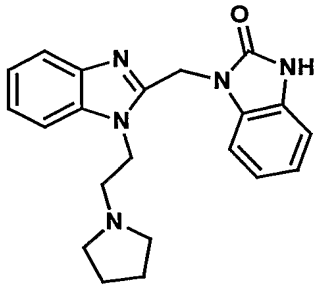
Compound 94



Compound **94** was prepared using the same procedure as compound **88** with N-(2-chloroethyl) pyrrolidine hydrochloride in 82% yield:

^{1}H NMR ($CDCl_3$) δ 1.70 (bs, 4H), 2.23 (s, 3H), 2.50 (bs, 4H), 2.66 (t, J = 7.0 Hz, 2H), 4.48 (t, J = 7.0 Hz, 2H), 5.20 (s, 1H), 5.37 (s, 1H), 5.39 (s, 2H), 7.02-7.09 (m, 3H), 7.24-7.35 (m, 2H), 7.35-7.40 (m, 1H), 7.47-7.50 (m, 1H), 7.75-7.80 (m, 1H);
IR (KBr, cm^{-1}) 2956, 2796, 1701, 1489, 1395, 1332, 1153, 743;
MS m/e 402 (MH^+);
Anal. Calcd for $C_{24}H_{27}N_5O$: C, 71.79; H, 6.78; N, 17.44
Found: C, 71.55; H, 6.84; N, 17.37

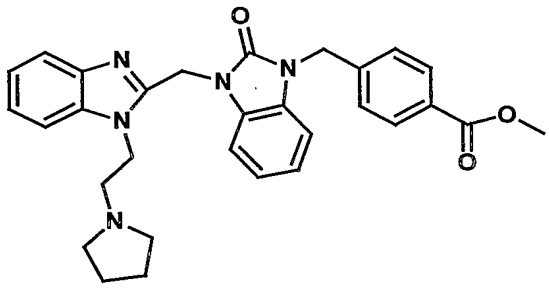
Compound 95



Compound **95** was prepared as described for compound **6**.

^{1}H NMR ($CDCl_3$) 1.62-1.80 (m, 4H), 2.46-2.59 (m, 4H), 2.67 (t, J = 7.2Hz, 2H), 4.47 (t, J = 7.4Hz. 2H), 5.40 (s, 2H), 7.00-7.04 (m, 3H), 7.25-7.29 (m, 2H), 7.36-7.43 (m, 2H), 7.76-7.93 (m, 1H), 8.68 (bs, 1H);
MS m/e 362 (MH^+).

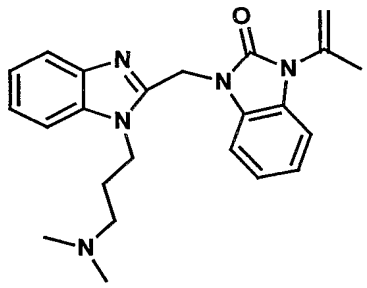
Compound 96



Compound **96** was prepared as described for compound **7**.

^{1}H NMR (CD_3OD) δ 2.02-2.33 (m, 4H), 3.22-3.33 (m, 2H), 3.78-3.89 (m, 2H), 3.90 (s, 3H), 3.94 (t, J = 7.9Hz, 2H), 5.21 (t, J = 7.2 Hz, 2H), 5.27 (s, 2H), 5.94 (s, 2H), 7.17- 7.25 (m, 3H), 7.49-7.53 (m, 3H), 7.69-7.81 (m, 3H), 8.02 (d, J = 8.2Hz, 2 H), 8.16 (d, J = 7.9 Hz, 1H);
MS m/e 362 (MH^+).

Compound 97

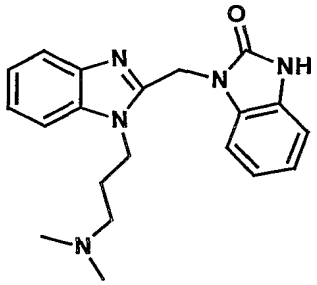


Compound **97** was prepared as described for compound **88** using 2-chloropropyldimethylamine hydrochloride.

^{1}H NMR ($CDCl_3$) δ 1.74-1.84 (m, 2H), 2.13 (s, 6H), 2.17 (t,J = 6.9 Hz, 2H), 2.23 (s, 3H), 4.41 (t, J = 7.1 Hz, 2H), 5.20 (s, 1H), 5.37 (d, J = 1.4 Hz, 1H), 5.44 (s, 2H), 6.98-7.08 (m, 3H), 7.22-7.28 (m, 2 H), 7.35-7.41 (m, 1H), 7.46-7.52 (m, 1H), 7.75-7.80 (m, 1H);

MS m/e 390 (MH^+).

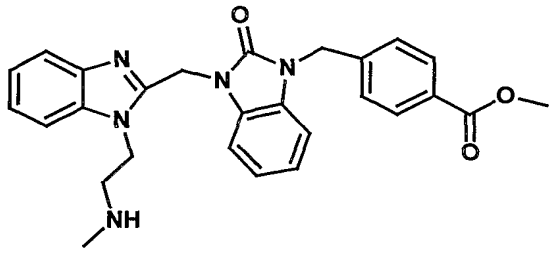
Compound 98



Compound **98** was prepared as described for compound **6**.

^1H NMR ($CDCl_3$) δ 1.76-1.85 (m, 2H), 2.23 (s, 6H), 2.33 (t, J = 7.1 Hz, 2H, 4.38 (t, J = 7.3 Hz, 2H), 5.43 (s, 28/H), 6.99-7.02 (m, 3H), .25-7.29 (m, 2H), 7.35-7.42 (m, 2H), 7.75-7.80 (m, 1H);
MS m/e 350 (MH^+).

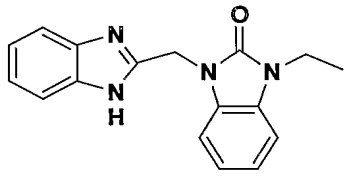
Compound 99



N-methylethanolamine was treated with benzylchloroformate to give (2-hydroxy-ethyl)-methyl-carbamic acid benzyl ester. The product was treated with methanesulfonyl chloride and Et_3N in CH_2Cl_2 to give methanesulfonic acid 2-(benzyloxycarbonyl-methyl-amino)-ethyl ester. The resulting mesylate is used to alklylate **3** as described for the preparation of **4**. The isopropenyl group is removed with acid as described for **6**. The product is alkylated as described for compound **7** and the benzyloxy group was removed with catalytic hydrogenation (Pd/C) to give compound **99**.

^{1}H NMR (CD_3OD) δ 2.86 (s, 3H), 3.79 (t, J = 6.7Hz, 2H), 3.90 (s, 3H), 5.16 (t, J = 6.7Hz, 2H), 5.26 (s, 2H), 5.96 (s, 2H), 7.19-7.26 (m, 3H), 7.51 (d, J = 8.3Hz, 3H), 7.68-7.80 (m, 3H), 8.01 (d, J = 8.3Hz, 2H), 8.14 (d, J = 8.2Hz, 1H);
MS m/e 470 (MH^+).

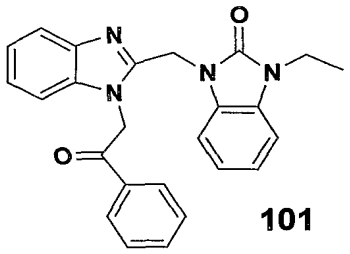
Compound 100 (Scheme I)



To a solution of 1-ethyl-2-benzimidazolone (0.5 g, 3.39 mmol) in DMF (10 mL) was added to NaH (136 mg, 3.39 mmol) and the mixture was stirred for 1 hr. 1-Methylsulfonyl-2-iodomethylbenzimidazole (2) (1.14 g, 3.39 mmol) was added and the mixture was stirred for 12 h. The reaction was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organic extracts were combined, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography, eluted with 50 % ethyl acetate in hexanes to give 767 mg (61% yield) of the N-methanesulfonylated derivative of **100a**. A mixture of the N-methanesulfonylated derivative of **100** (760 mg, 2.0 mmol) and hydrazine hydrate (0.9 ml) in methanol was heated to reflux for 12h, then cooled and concentrated. The residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by chromatography on silica gel with 50% ethyl acetate in hexanes as eluant to give 250 mg (28%) of compound **100** as a white solid.

^{1}H NMR (DMSO-d6) δ 1.26 (t, J = 7.1 Hz, 3H), 3.93 (q, J = 7.1 Hz, 2H), 5.27 (s, 2H), 6.99 (t, J = 7.4 Hz, 1H), 7.05-7.06 (m, 2H), 7.07-7.08 (m, 2H), 7.24 (d, J = 8.3 Hz, 1H), 7.40-7.60 (m, 2H);
MS m/e 292 (MH^+).

Compound 101



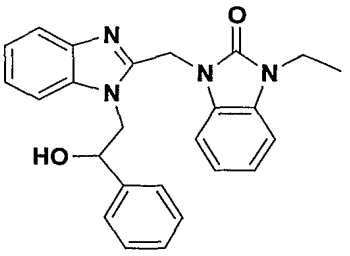
101

Compound **100** (500 mg, 1.71 mmol) in DMF (2 mL) was added to a slurry of sodium hydride (60% in mineral oil, 75 mg, 3.14 mmol) in DMF (10 ml) and stirred for 1 h. 2-Bromoacetophenone (375 mg, 1.88 mmol) was added and the mixture was stirred for 48 h. The reaction was diluted with water and extracted with ethyl acetate. The organic extracts were combined, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography with 50% ethyl acetate in hexanes as eluant to give 474 mg (68% yield) of compound **101** as a white solid:

^{1}H NMR (DMSO-d_6) δ 1.05 (t, J = 7.1 Hz, 3 H), 3.65 (q, J = 7.1 Hz, 2 H), 5.28 (s, 2 H), 6.15 (s, 2 H), 7.00-7.05 (m, 2 H), 7.13-7.20 (m, 3 H), 7.24-7.27 (m, 1 H), 7.44-7.49 (m, 1 H), 7.60-7.65 (m, 3 H), 7.73-7.95 (m, 1 H), 8.03 (d, J = 8.4 Hz, 2 H);
IR (KBr, cm^{-1}) 2956, 1706, 1686, 1497, 1219, 744;
MS m/e 411 (MH^+);

Anal. Calcd for $C_{25}H_{22}N_4O_2 \bullet 0.4\ H_2O$: C, 72.20; H,5.48; N, 13.47
Found: C, 72.04; H, 5.45; N, 13.66.

Compound 102



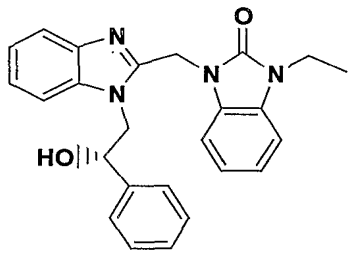
To a 0°C solution of compound **101** (350 mg, 0.85 mmol) in MeOH (10 ml) was added $NaBH_4$ (323 mg, 8.53 mmol) and the mixture stirred for 2 h. The reaction was warmed to 23°C and stirred for 12 h. The solvent was evaporated and the residue dissolved in EtOAc and washed with water. The organic layer is dried over Na_2SO_4

and concentrated. The residue was purified by flash chromatography with 50% EtOAc in hexanes to give 264 mg (75%) of compound **102** as a white solid.

^{1}H NMR (DMSO-d_6) δ 1.22 (t, J = 7.1 Hz, 3H), 3.91 (q, J = 6.9 Hz, 2H), 4.42-4.61 (m, 2H), 4.90-4.91 (m, 1H), 5.26-5.31 (m, 1H), 5.40-5.46 (m, 1H), 5.82-5.83 (m, 2H), 6.97-7.08 (m, 2H), 7.15-7.29 (m, 4H), 7.32-7.42 (m, 3H), 7.39-7.61 (m, 4H);
IR (KBr, cm^{-1}) 3200, 1701, 733;
MS m/e 412 (MH^+);

Anal. Calcd for $C_{25}H_{24}N_4O_2 \bullet 0.16\ H_2O$: C, 72.29; H,5.90; N, 13.49
Found: C, 72.27; H, 5.72; N, 13.33.

Compound 103



To a stirred solution of compound **100** (150 mg, 0.51 mmol) in DMF (10 ml) was addedsodium hydride (22.6 mg, 0.55 mmol) and the mixture sitrred for 1 hour. R-(+)-styrene oxide (123 mg, 1.02 mmol) was added and the mixture heated to 110°C for 2 h. The mixture was cooled, diluted with water and extracted with EtOAc. The combined organic extracts are dried over Na_2SO_4 and concentrated. The residue is purified by flash chromatography to give compound **103** (34 mg, 16%) as a white solid.

^{1}H NMR (DMSO-d_6) δ 1.22 (t, J = 7.1 Hz, 3H), 3.91 (q, J = 6.9 Hz, 2H), 4.43-4.61 (m, 2H), 4.90-4.93 (m, 1H), 5.16-5.31 (m, 1H), 5.33-5.46 (m, 1H), 5.82-5.83 (m, 2H), 6.97-7.08 (m, 2H), 7.15-7.29 (m, 4H), 7.32-7.42 (m, 3H), 7.39-7.61 (m, 4H);

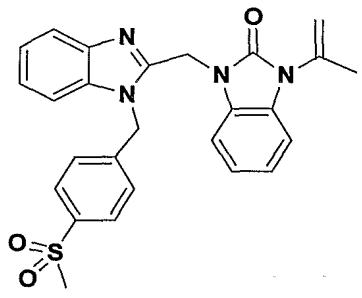
$[a]_D^{25}$ = -44.76 (25°C, c = 0.714, CH_2Cl_2)

MS m/e 412 (MH^+);

Anal. Calcd for $C_{25}H_{24}N_4O_2$: C, 72.80; H,5.86; N, 13.58

Found: C, 72.50; H, 6.21; N, 12.52.

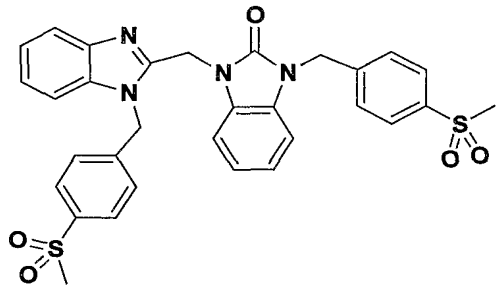
Compound 104



Compound **104** was prepared by alklylation of compound **100** with 1-methanesulfonyl-4-chloromethyl-benzene as previously described for compound **101**.

^{1}H NMR (DMSO-d6) δ 1.96 (s, 3 H), 3.12 (s, 3 H), 4.94 (s, 1 H), 5.19 (s, 1 H), 5.42 (s, 2 H), 5.77 (s, 2 H), 6.95 (d, J = 5.0, 2 H), 7.02-7.07 (m, 3 H), 7.20-7.25 (m, 3 H), 7.61-7.63 (m, 2H), 7.68-7.71 (m, 1H), 7.90-7.98 (m, 1H);
MS m/e 473 (MH^+).

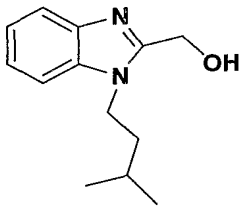
Compound 105



The isopropenyl group of compound **104** was removed as described for compound **6** and converted to compound **105** as described for compound **7** using 1-methanesulfonyl-4-chloromethylbenzene.

^{1}H NMR (DMSO-d6) δ 3.17 (s, 6H), 4.99 (s, 2H), 5.47 (s, 2H), 5.79 (s, 2H), 6.98-7.03 (m, 3H), 7.07 (d, J = 5.0, 2H), 7.17 (d, J = 5.5, 1H), 7.25-7.27 (m, 2H), 7.47-7.53 (m, 1H), 7.51 (d, J = 4.1, 2H), 7.69-7.72 (m, 2H), 7.88 (d, J = 5.0, 2H);
MS m/e 600 (MH^+).

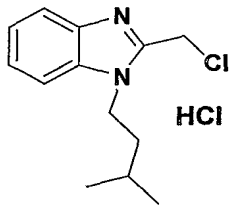
Compound 106 (Scheme II)



To a solution of 2-hydroxymethylbenzimidazole (27.1 g, 182.9 mmol) in a 1:1 mixture of DMF/THF (200 mL) was added NaH (60% in mineral oil, 8.05 g, 201.2 mmol) at room temperature. After stirring for 1.5 h, 1-bromo-3-methylbutane (29 g, 192 mmol) was added and the mixture was stirred at 75 °C overnight. The mixture was adjusted to neutral pH with concentrated HCl and the solvent was evaporated. The residue was diluted with EtOAc, washed with water, dried over

$MgSO_4$, and evaporated. The residue was crystallized from EtOAc/hexane to give 29 g of compound **106** as white solid. The mother liquor was purified by flash chromatography (EtOAc:hexane= 1:1 to 2:1 and then EtOAc:MeOH = 10:0 to 10:1) to give additional 5.24 g (total 86% yield) of compound **106**.

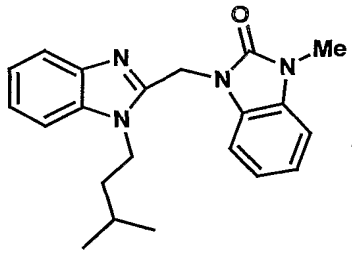
Compound 107



To a solution of compound **106** (34.24g, 156.9 mmol) in CH_2Cl_2 (100 mL) was slowly added $SOCl_2$ (28 g, 235.4 mmol) with an ice-bath cooling. The resulting solution was stirred at room temperature for 1 h and evaporated. The residue was dried in vacuum and then triturated in a mixture of CH_2Cl_2/Et_2O to give 41.25 g (96% yield) of compound **107** as a white solid:

^1H NMR (DMSO-d_6) δ 0.99 (d, J = 6.3 Hz, 6H), 1.72-1.79 (m, 3H), 4.47-4.52 (m, 2H), 5.36 (s, 2H), 7.52-7.61 (m, 2H), 7.82-7.92 (m, 2H);
MS m/e 237 (MH^+).

Compound 108



A mixture of **107** (200 mg, 0.84 mmol), N-methylbenzimidazole (128 mg, 0.76 mmol) and NaH (33.6 mg, 0.84 mmol) were stirred in acetonitrile (10 mL) for 1 h. The solvent was evaporated. The residue was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by chromatography to give 65.9 mg (25% yield) of compound **108**:

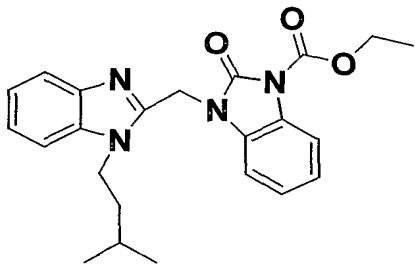
^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 6 H), 1.28-1.36 (m, 2 H), 1.61-1.74 (m, 1 H), 3.45 (s, 3 H), 4.26-4.32 (m, 2 H), 5.42 (s, 2 H), 6.93-7.10 (m, 3 H), 7.27-7.32 (m, 3 H), 7.40 (d, J = 7.4 Hz, 1 H), 7.79-7.81 (m, 1 H);

IR (KBr, cm^{-1}) 3425, 3054, 1706, 1499, 1399, 743;

MS m/e 349 (MH^+);

Anal. Calcd for $C_{21}H_{24}N_4O_1 \bullet 0.65\ H_2O$: C, 70.03; H, 7.08; N, 15.56.
Found: C, 70.05; H, 6.83; N, 15.45.

Compound 109

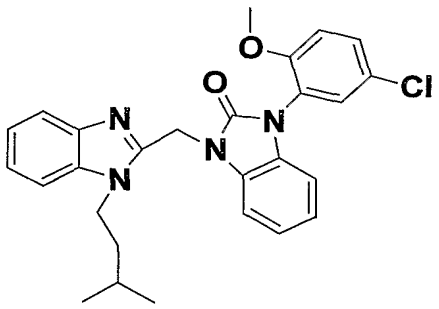


Compound **109** was prepared from the known 1-carboethoxy-benzimidazolone (Meanwell et al J. Org. Chem. 1995, 60, 1565-1582) and **107** as described above for the preparation of **108**.

^{1}H NMR $CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.37-1.45 (m, 2H), 1.50 (t, J = 7.1 Hz, 3H), 1.67-1.74 (m, 1H), 4.29-4.35 (m, 2H), 5.38 (s, 2H), 7.10-7.19 (m, 2H), 7.29-7.33 (m, 3H), 7.47-7.50 (m, 1H), 7.77-7.80 (m, 1H), 7.83-7.86 (m, 1H);

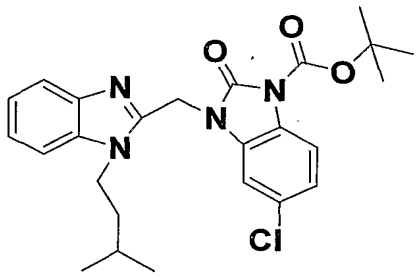
MS m/e 407 (MH^+).

Compound 110



^{1}H NMR ($CDCl_3$) δ 0.94 (dd, J = 1.3, 6.6 Hz, 6H), 1.44-1.74 (m, 3H), 3.76 (s, 3H), 4.32-4.38 (m, 2H), 5.46 (s, 2H), 6.67 (d, J = 7.5 Hz, 1H), 6.97-7.09 (m, 3H), 7.27-7.43 (m, 5H), 7.54 (d, J = 7.6 Hz, 1H), 7.78-7.83 (m, 1H).

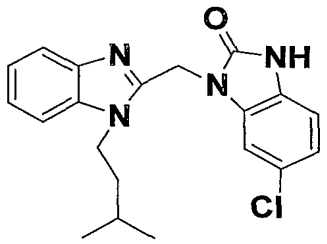
Compound 111



Compound **111** was prepared in 49% yield by the same procedure as described for compound **108** with chloride **107** and N-t-butoxycarbonyl-5-chlorobenzimidazolone (Meanwell et al J. Org. Chem. 1995, 60, 1565-1582):

^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.7 Hz, 6H), 1.39-1.45 (m, 2H), 1.66 (s, 9H), 1.64-1.77 (m, 1H), 4.29-4.35 (m, 2H), 5.37 (s, 2H), 7.07 (dd, J = 2.0, 8.,6 Hz, 1H), 7.28-7.33 (m, 3H), 7.56 (bs, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.80-7.82 (m, 1H);
IR (KBr, cm^{-1}) 2871, 1791, 1752, 1489, 1378, 1323, 1253, 1149, 1113, 742.
MS m/e 469 (MH^+);
Anal. Calcd for $C_{25}H_{29}ClN_4O_3$: C, 64.03; H, 6.23; N, 11.95
Found: C, 64.29; H, 6.02; N, 11.55.

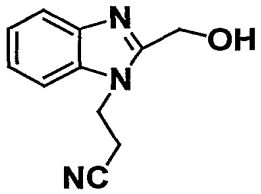
Compound 112



Compound **111** (200 mg, 0.43 mmol) was dissolved in a mixture of CH_2Cl_2:TFA (3:1, 4 mL). The mixture was stirred at ambient temperature for 5 minutes and then evaporated. The residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, water, and dried over $MgSO_4$. The residue was purified by chromatography (EtOAc: hexane 1:1 to 2:1) to give compound 18 mg of the compound **112** as a light yellow solid:

^{1}H NMR (DMSO-d_6) δ 0.94 (d, J = 6.6 Hz, 6H), 1.41-1.48 (m, 2H), 1.63-1.72 (m, 1H), 4.30 (bt, J = 8.1 Hz, 2H), 5.34 (s, 2H), 7.04 (s, 2H), 7.12-7.27 (m, 3H), 7.52 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H);
IR (KBr, cm^{-1}) 2956, 1705, 1489, 1458, 1386, 741;
MS m/e 369 (MH^+);
Anal. Calcd for $C_{20}H_{21}ClN_4O \bullet 0.4\ CF_3COOH$: C, 60.28; H,5.20; N, 13.52.
Found: C, 60.49; H, 5.58; N, 13.41.

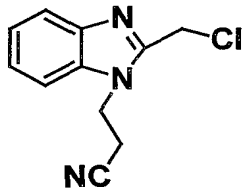
Compound 113



Compound **113** was prepared using Michael addition conditions described by Popov, I. I. in Khim Geterotskl. Soedin. 1996 (6), 781-792.

^{1}H NMR ($CDCl_3$) δ 3.08 (t, J = 6.8 Hz, 2H), 4.63 (t, J = 6.8 Hz, 2H), 4.77 (d, J = 5.7 Hz, 2H), 5.73 (t, J = 5.7 Hz, 1H), 7.17-7.28 (m, 2H), 7.64 (d, J = 1.2 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H);
MS m/e 202 (MH^+);
Anal. Calcd for $C_{11}H_{11}N_3O$: C 65.66; H, 5.51; N, 20.88.
Found: C, 65.94; H, 5.57; N, 21.08.

Compound 114

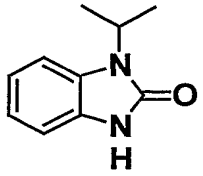


114

To a solution of alcohol **113** (20g, 99.4 mmol) in methylene chloride (50 mL) was slowly added $SOCl_2$ (15.4 g, 129.2 mmol). The solution was stirred at room temperature for 3 hours. The solvent was evaporated. The residue was diluted with water and neutralized with saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated. The residue was triturated with Et_2O and hexane to give 19.78 g (91% yield) of compound **114** as a white solid:

^{1}H NMR ($CDCl_3$) δ 3.02 (t, J = 7.0Hz, 2H), 4.65 (t, J = 7.0 Hz, 2H), 4.99 (s, 2H), 7.34-7.44 (m, 3H), 7.79-7.82 (m, 1H);
MS m/e 220 (MH^+);
Anal. Calcd for $C_{11}H_{10}ClN_3$: C, 60.09; H, 4.65; N, 19.13.
Found: C, 60.09; H, 4.65; N, 19.11.

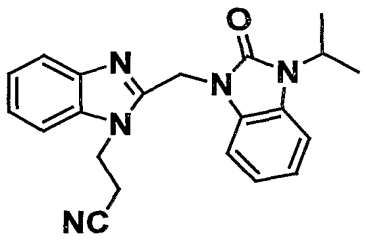
Compound 115



A mixture of N-isopropenyl-2-benzimidazolone (6.90 g, 39.6 mmol) and 1 g of 10 % palladium on carbon in 30 mL of methanol was hydrogenated at 45-55 psi for one hour. The catalyst was filtered and the filtrate was evaporated to give quantitative yield of compound **115** as a white solid:

^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 7.1 Hz, 6H), 4.70-4.81 (m, 1H), 7.02-7.10 (m, 2H), 7.10-7.20 (m, 2H);
MS m/e 177 (MH^+);
Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90
Found: C, 68.05; H, 6.63; N, 15.77.

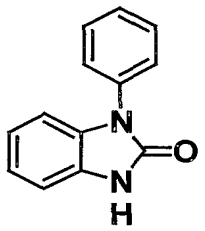
Compound 116



To compound **115** (5.0 g, 28.37 mmol) and chloride **114** (6.23 g, 28.37 mmol) in THF (50 mL) was added BTPP (7.39 g, 42.6 mmol) at room temperature and stirred for 30 minutes. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc : hexane 1:2 to 2:1) to give 7.62 g (75%) of compound **116** as a white solid:

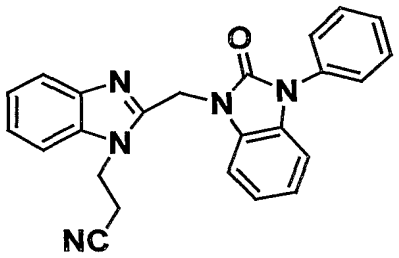
^{1}H NMR ($CDCl_3$) δ 1.58 (d, J = 7.0 Hz, 6H), 2.68 (t, J = 6.8 Hz, 2H), 4.71-4.83 (m, 1H), 4.81 (t, J = 6.8 Hz, 2H), 5.40 (s, 2H), 7.06-7.27 (m, 3H), 7.34-7.40 (m, 3H), 7.57-7.61 (m, 1H), 7.82-7.87 (m, 1H);
IR (KBr, cm^{-1}) 2250, 1694, 1493, 1396, 745;
MS m/e 360 (MH^+);
Anal. Calcd for $C_{21}H_{21}N_5O \bullet 0.3\ H_2O$: C, 69.14; H, 5.97; N, 19.20
Found: C, 69.07; H, 5.92; N, 19.40.

Compound 117



2-fluoronitrobenzene was treated with aniline in the prescence of K_2CO_3 in CH_3CN and heated to reflux for 12 h. The solution is cooled, filtered and the solvent removed. The nitro group is reduced with catalytic hydrogenation and the diamine treated with CDI to give 1-phenyl-1,3-dihydro-benzoimidazol-2-one.

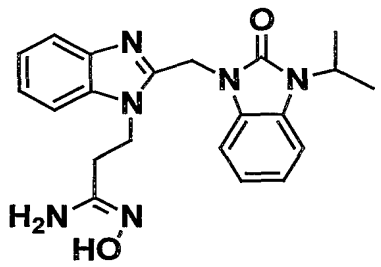
Compound 118



Compound **118** was prepared by alkylation of compound **117** with compound **114** as described for compound **7**.

^{1}H NMR ($CDCl_3$) δ 2.82 (t, J = 6.5 Hz, 2H), 4.86 (t, J = 6.5 Hz, 2H), 5.56 (s, 2H), 7.08-7.21 (m, 3H), 7.34-7.39 (m, 3H), 7.44-7.47 (m, 1H), 7.54-7.57 (m, 4H), 7.72 (d, J = 7.8 Hz, 1H), 7.85-7.89 (m, 1H);
MS m/e 393 (MH^+).

Compound 119

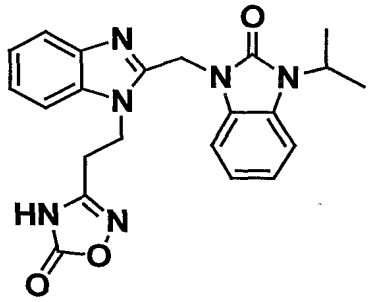


Nitrile **116** (4.6 g, 12.80 mmol), hydroxylamine hydrochloride (3.2 g, 46.07 mmol), and potassium carbonate (3.5 g, 25.60 mmol) were suspended in ethanol / water (100 mL/ 50 mL). This mixture was stirred at near reflux (60-80 °C) for 16 hours. The solvent was evaporated. To the residue, water was added to dissolve any inorganic salts. The white solid was filtered and washed with water. The solid was triturated with EtOAc to give 5.0 g (quantitative yield) of compound **119** as a white solid.

^{1}H NMR (DMSO-d_6) δ 1.47 (d, J = 6.9 Hz, 6H), 2.39 (t, J =6.8 Hz, 2H), 4.56 (t, J = 6.8 Hz, 2H), 4.61-4.70 (m, 1H), 5.35 (s, 2H), 6.61 (s, 2H),6.98-7.06 (m, 2H), 7.12-7.24 (m, 3H), 7.33 (d, J = 7.1 Hz, 1H), 7.54 (t, J = 8.4 Hz, 2H), 8.96 (s, 1H);
IR (KBr, cm^{-1}) 3470, 3332, 1698, 1680, 1663, 1491, 1430, 750;
MS m/e 393 (MH^+);

Anal. Calcd for $C_{21}H_{24}N_6O_2 \bullet 2.75\ H_2O$: C, 57.07; H, 6.73; N, 19.01
Found: C, 57.43; H, 6.43; N, 18.79.

Compound 120



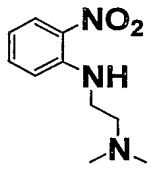
Amidoxime **119** (4.0 g, 10.19 mmol) was suspended in a toluene solution of phosgene (1.92M , 53 mL, 101.92 mmol). The reaction mixture was heated to reflux

(120 °C) for 8 hours under nitrogen. The solvent was evaporated. The residue was taken up in water and the pH was adjusted to 5 by addition of saturated sodium bicarbonate. The aqueous mixture was then extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Recrystallization of 4 g of the crude product in hot EtOAc (400-500 mL) gave compound **120** as fine white needles (3.0 g, 75% recovery, 71% yield from **119**):

To a solution of compound **120** (1.58 g, 3.77 mmol) in MeOH (10 mL) was added 1N NaOH (3.77 mL, 3.77 mmol) and evaporated. The residue was taken up in water and filtered. The filtrate was lyophilized to give the sodium salt of compound **120** as an amorphous fluffy white solid (1.56 g, 94% yield):

^{1}H NMR (DMSO-d_6) δ 1.46 (d, J = 7.0 Hz, 6H), 2.67 (t, J = 6.7 Hz, 2H), 4.59-4.68 (m, 3H), 5.35 (s, 2H), 6.94-7.05 (m, 2H), 7.14-7.23 (m, 3H), 7.32 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 6.8 Hz, 2H);
IR (KBr, cm^{-1}) 3406, 2978, 1686, 1490, 1408, 750;
MS m/e 511 (MH^+);
Anal. Calcd for $C_{22}H_{22}N_6NaO_3$: C, 59.86; H, 5.02; N, 19.04
Found: C, 59.68; H, 5.00; N, 18.78

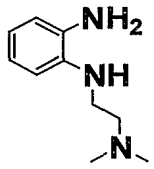
Compound 121 (Scheme II)



To a mixture of 2-fluoronitrobenzene (16.8 g, 119 mmol) and sodium acetate (300 mg) was added N,N-dimethylethylenediamine (12.5 mL, 113 mmol). After heating to 80 °C for 1 h, the mixture was poured into water, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by silica gel chromatography (gradient, 1:1 EtOAc:Hexanes to 5% MeOH in EtOAc) to provide 12.0 g (50% yield) of compound **121** as an orange oil.

^{1}H NMR ($CDCl_3$) δ 2.31 (s, 6H), 2.64 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H), 6.63 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.40-7.45 (m, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.29-8.39 (m, 1H);
MS m/e 209 (MH^+).

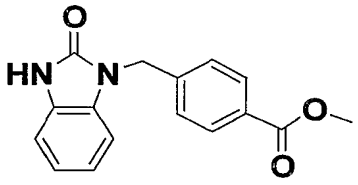
Compound 122



A mixture of compound **121** (10.0 g, 47.7 mmol) and 10% Pd/C (500 mg) in ethanol (100 mL) was hydrogenated at 50 psi for 1 h. The mixture was filtered through a pad of celite and the filtrate was evaporated. The residue was recrystallized from hexanes to give 7.52 g (88%) of a flaky brown solid of compound **122**.

^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6H), 2.59 (t, J = 6.0 Hz, 2H), 3.15 (t, J = 6.0 Hz, 2H), 6.65-6.72 (m, 3H), 6.79-6.82 (m, 1H);
MS m/e 179 (MH^+).

Compound 123

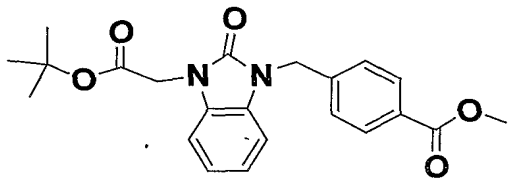


A mixture of ethyl 2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylate (5 g, 24.3 mmol), K_2CO_3 (3.35 g, 24.3 mmol) and methyl 4-bromomethyl-benzoate (5.56 g, 24.3 mmol) was stirred in acetonitrile (100 mL) at reflux for 3 h. The mixture was filtered and the filtrate was concentrated. The oily residue was dissolved in methanol (50 mL), treated with sodium methoxide in methanol (1.0 mL, 0.5 M) and stirred for 12 h. The product precipitated from the solution was filtered to give 5.88 g (99% yield) of compound **123** as white solid:

^{1}H NMR (DMSO-d_6) δ3.82 (s, 3H), 5.09 (s, 2H), 6.95-6.99 (m, 4H), 7.42 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H);

IR (KBr, cm^{-1}) 3464(br), 1718, 1696;
MS m/e 283 (MH^+);
Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92.
Found: C, 67.85; H, 5.01; N, 9.84.

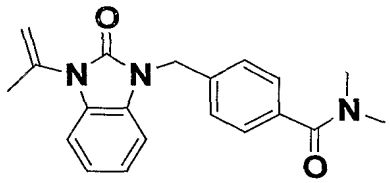
Compound 124



A mixture of **123** (5.8 g, 27.6 mmol), t-butyl bromoacetate (4.1 mL, 27.6 mmol) and potassium carbonate (3.8 g, 27.6 mmol) in acetonitrile (100 mL) was heated to reflux for 3 h. The mixture was cooled to room temperature, filtered and concentrated to give 9.58 g (88% yield) of compound **124** as a white solid:

^1H NMR (DMSO-d_6) δ 1.41 (s, 9H), 3.83 (s, 3H), 4.66 (s, 2H), 5.17 (s, 2H), 7.02-7.18 (m, 4H), 7.42 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H);
IR (KBr, cm^{-1}) 1742, 1721, 1715;
MS m/e 397 (MH^+).

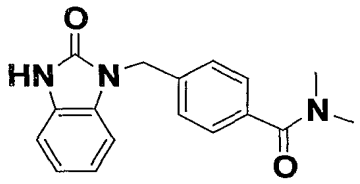
4-(3-Isopropenyl-2-oxo-2,3-dihydro-benzoimidazol-1-ylmethyl)-N,N-dimethyl-benzamide



4-(3-Isopropenyl-2-oxo-2,3-dihydro-benzoimidazol-1-ylmethyl)-N,N-dimethyl-benzamide was prepared from 1-isopropenyl-1,3-dihydro-benzoimidazol-2-one and compound **90** as described for compound **7**.

^1H NMR (CD_3OD) δ 2.21 (s, 3H), 2.96 (s, 3H), 3.07 (s, 3H), 5.15 (s, 2H), 5.23 (s, 1H), 5.45-5.46 (m, 1H), 7.05-7.12 (m, 3H), 7.17-7.18 (m, 1H), 7.39-7.43 (m, 4H);
MS m/e 336 (MH^+).

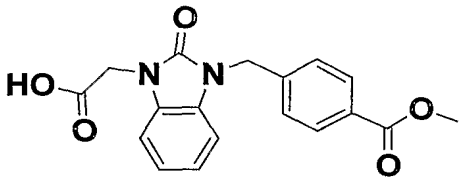
N,N-Dimethyl-4-(2-oxo-2,3-dihydro-benzoimidazol-1-ylmethyl)-benzamide



N,N-Dimethyl-4-(2-oxo-2,3-dihydro-benzoimidazol-1-ylmethyl)-benzamide was prepared as described for compound **6**.

^{1}H NMR (DMSO-d6) δ 2.86 (s, 3 H), 2.95 (s, 3H), 5.04 (s, 2H), 6.94-7.05 (m, 4H), 7.33-7.37 (m, 4H);
MS m/e 296 (MH^+).

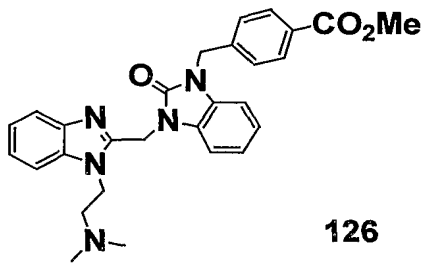
Compound 125



Ester **124** (5.4 g, 13.6 mmol) was stirred in trifluoroacetic acid (50 mL) at room temperature for 12 h. The mixture was evaporated to give 4.0 g (87% yield) of compound **125** as a light yellow solid:

^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3H), 4.72 (s, 2H), 5.22 (s, 2H), 7.06-7.24 (m, 3H), 7.17-7.27 (m, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H);
IR (KBr, cm^{-1}) 3464(br), 1738, 1720, 1666;
MS m/e 341 (MH^+);
Anal. Calcd for $C_{18}H_{16}N_5O \cdot 0.86\ H_2O$: C, 57.67; H, 4.69; N, 7.26.
Found: C, 57.67; H, 4.29; N, 6.95.

Compound 126

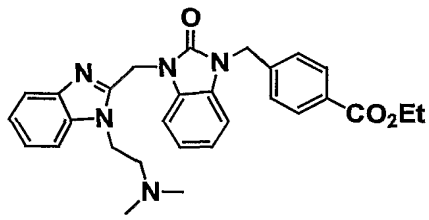


126

Compound **122** (1.32 g, 7.35 mmol) and benzimidazolone **125** (2.5 g, 7.35 mmol) were dissolved in DMF (8 mL). To the solution EDC (3.18 g, 16.2 mmol) was added and the resulting mixture was stirred for 18 h under nitrogen. The mixture was poured into water and extracted into EtOAc. The extracts were dried over $MgSO_4$ and evaporated. The gummy residue was dissolved in 20 mL of acetic acid and the solution was heated to reflux for 6 h. The mixture was evaporated and the residue was diluted with EtOAc, washed with water, dried over $MgSO_4$ and evaporated. The gummy residue was triturated with EtOAc to produce 255 mg (7% yield) of compound **126**. A portion of the material was converted to the HCl salt with excess HCl in dioxane and the volatile components were removed in vacuo:

^{1}H NMR (DMSO-d_6) δ 3.12, 3.33 (s, 6H), 4.00 (m, 2H), 4.25 (s, 3H), 5.39 (m, 2H), 5.65 (s, 2H), 6.10 (s, 2H), 7.49 (m, 2H), 7.57 (m, 1H), 7.81 (m, 4H), 7.92 (d, J = 8.1 Hz, 2H), 8.08 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 8.1 Hz, 2H), 11.67 (s, 1H);
IR (KBr, cm^{-1}) 3421, 2952, 1708, 1491, 1407, 1280, 750;
MS m/e 484 (MH^+);
Anal. Calcd for $C_{28}H_{29}N_5O_3 \cdot 2.25$ HCl: C, 59.22; H, 5.56; N, 12.33.
Found: C, 59.22; H, 5.42; N, 12.01.

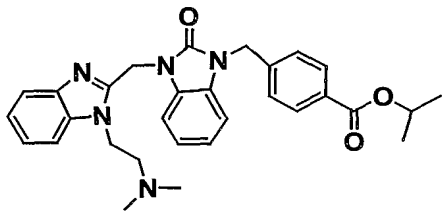
Compound 131



Sodium ethoxide was prepared by dissolving fresh cut sodium (0.2 g, 8.40 mmol) in anhydrous EtOH (10 mL). To a solution of methyl ester, compound **126**, (1.2 g, 2.48 mmol) in anhydrous EtOH (300 mL) was added the ethanolic sodium ethoxide solution. The reaction mixture was stirred at reflux for 1 hour and the solution was adjusted to pH 1 with 4 N HCl in dioxane. The solvent was evaporated. The residue was purified by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) and treated with excess 4 N HCl in dioxane to give 1.07 g (87% yield) of compound **131** as the HCl salt:

^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.2Hz, 3H), 2.26 (s, 6H), 2.51 (t, J = 6.9Hz, 2H), 4.36 (q, J = 7.2Hz, 2H), 4.45 (t, J = 6.9Hz, 2H), 5.16 (s, 2H), 5.47 (s, 2H), 6.80 (d, J = 7.5Hz, 1H), 6.98-7.04 (m, 2H), 7.28-7.35 (m, 2H), 7.28-7.35 (m, 4H), 7.38 (d, J = 8.4Hz, 1H), 7.52 (d, J = 7.2Hz, 1H), 7.78-7.81 (m, 1H), 8.00 (d, J = 8.1Hz, 2H); MS m/e 498 (MH^+).

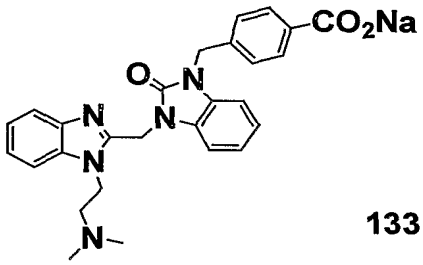
Compound 132



As described for compound **131**, the isopropyl derivative **132** was prepared from compound **126** using sodium isopropoxide.

^{1}H NMR (DMSO-d6) δ 1.29 (d, J = 6.2Hz, 6H), 2.89 (s, 3H), 2.91 (s, 3H), 4.93 (t, J = 7.8Hz, 2H), 5.07-5.15 (m, 1H), 5.22 (s, 2H), 5.63 (s, 2H), 7.02-7.14 (m, 3H), 7.32-7.40 (m, 3H), 7.48 (d, J = 8.3Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.87-7.93 (m, 3H); MS m/e 512 (MH^+).

Compound 133

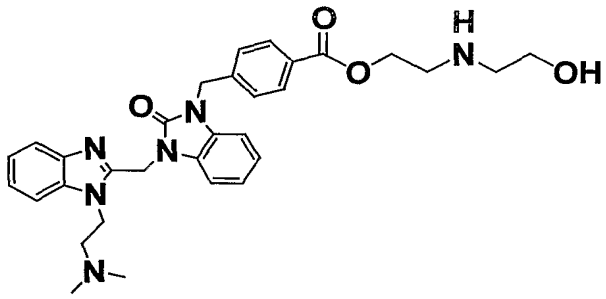


133

Compound **133** was prepared as a white powder in 71% yield using the same procedure as compound **8**:

^{1}H NMR (DMSO-d_6) δ 2.18 (s, 6H), 3.30-3.50 (m, 2H), 4.43 (t, J = 6.3 Hz, 2H), 5.09 (s, 2H), 5.44 (s, 2H), 6.95-7.00 (m, 2H), 7.08-7.25 (m, 1H), 7.52-7.57 (m, 5H), 7.54 (t, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H).
IR (KBr, cm^{-1}) 3422, 1702, 1599, 1557, 1395, 750;
MS m/e 470 (MH^+);
Anal. Calcd for $C_{27}H_{26}N_5O_3Na \cdot 2.1NaOH \cdot 2.0\ H_2O$:
C, 52.88; H, 5.28; N, 11.42.
Found: C, 53.10; H, 4.88; N, 11.02.

Compound 134

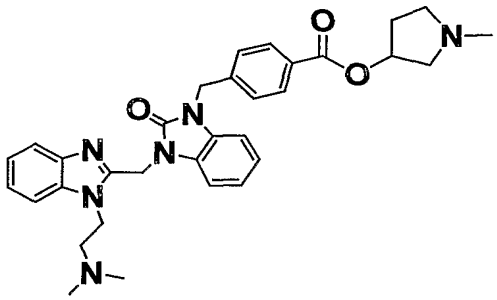


Compound **134** was prepared from compound **133** using PyBroP and 2-aziridin-1-yl-ethanol. The aziridine ring was opened during preparative HPLC with MeOH/H_2O with 1% TFA as buffer.

^{1}H NMR (DMSO-d6) 2.90-2.92 (m, 6H), 3.08-3.08 (m, 2H), 3.37 (s, 2H), 3.63 (s, 2H), 3.71-3.76 (m, 2H), 4.54 (t, J = 4.8Hz, 2H), 5.02 (t, J = 7.4Hz, 2H), 5.25 (s, 2H),

5.72-5.77 (m, 2H), 7.06-7.15 (m, 3H), 7.38-7.7.70 (m, 5H), 7.70 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.1Hz, 2H), 9.79 (m, 1H), 11.59 (m, 1H); MS m/e 557 (MH^+).

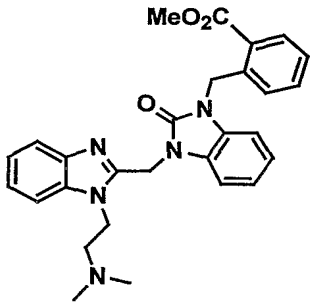
Compound 135



Compound **135** was prepared from compound **133** using PyBroP 1-methyl-3-hydroxylpyyrolidine.

^1H NMR (CD_3OD) δ 2.28-2.81 (m, 2H), 3.02 (s, 2H), 3.07 (s, 1H), 3.12 (s, 6H), 3.86-3.91 (m, 4H), 5.23 (t, J = 8.2Hz, 2H), 5.29 (s, 2H), 5.64-5.69 (m, 1H), 5.94 (s, 2H), 7.16-7.23 (m, 3H), 7.49-7.55 (m, 3H), 7.69-7.82 (m, 3H), 8.07-8.17 (m, 3H); MS m/e 553 (MH^+).

Compound 136

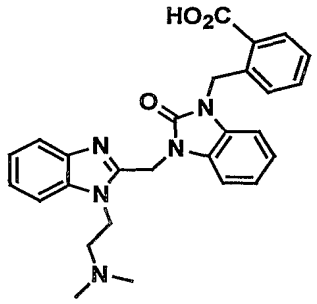


Compound **136** was prepared using the same procedure as compound **126**:

^1H NMR ($CDCl_3$) δ 2.31 (bs, 6H), 2.58 (bs, 2H), 3.97 (s, 3H), 4.52 (bs, 2H), 5.50 (s, 2H), 5.60 (s, 2H), 6.81 (d, J = 6.8 Hz, 1H), 6.98-7.09 (m, 3H), 7.28-7.42 (m, 5H), 7.80-7.83 (m, 1H), 8.07 (dd, J = 1.4, 7.4 Hz, 1H);

IR (KBr, cm^{-1}) 1717, 1702, 1497, 1417, 1261, 742;
MS m/e 484(MH^+).

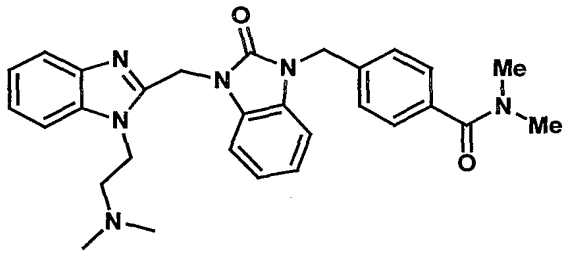
Compound 137



Compound **137** was prepared using the same procedure as compound **133**:

^1H NMR (CD_3OD) δ 2.28 (s, 6 H), 2.59 (t, J = 6.9 Hz, 2 H), 4.50 (t, J = 6.9 Hz, 2 H), 5.20 (s, 2 H), 5.30 (s, 2 H), 6.98-7.08 (m, 4 H), 7.18-7.32 (m, 5 H), 7.64-7.68 (m, 2 H);
IR (KBr, cm^{-1}) 1699, 168, 1586, 1560, 1492, 1395, 742;
MS m/e 470 (MH^+);
Anal. Calcd for $C_{27}H_{27}N_5NaO_3 \bullet .75H_2O$: C, 64.09; H, 5.68; N, 13.84
Found: C, 63.96; H, 5.49; N, 13.74

Compound 138



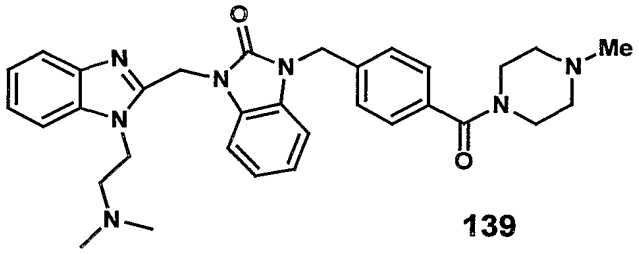
To a solution of acid **133** (704 mg, 1.5 mmol), N,N-dimethylamine hydrochloride salt (183 mg, 2.25 mmol), and diisopropylethylamine (386 mg, 3.0 mmol) in DMF (10 mL) was added PyBroP (769 mg, 1.65 mmol) in one portion at the ambient temperature. After stirring overnight, the resulting solution was concentrated. The residue was purified by prep-HPLC to furnish 660 mg (89% yield)

of compound **138** as white solid. To a solution of this solid (660 mg, 1.33 mmol) in methanol (20 mL) was added 4 N HCl in 1,4-dioxane (0.66 mL, 2.66 mmol). The resulting hydrochloride salt precipitated out of solution and was collected by filtration to yield 650 mg (92% yield) of dihydrochloride salt of compound **138** as white crystals:

^{1}HNMR (CD_3OD) δ 2.99 (s, 3H), 3.10 (s, 3H), 3.12 (s, 6H), 3.87 (t, J = 7.5 Hz, 2H), 5.23 (t, J = 7.5 Hz, 2H), 5.24 (s, 2H), 5.94 (s, 2 H), 7.20-7.23 (m, 3 H), 7.43 (d, J = 8.2 Hz, 2H), 7.48-7.52 (m, 3H), 7.70-7.81 (m, 3H), 8.16 (d, J = 8.3 Hz, 1H);
IR (KBr, cm^{-1}) 3422, 1702, 1614, 1493, 1406, 1181, 753;
MS m/e 497 (MH^+);

Anal. calcd for $C_{29}H_{33}ClN_6O_2 \bullet 2.0HCl \bullet 1.0TFA \bullet 1.5H_2O$:
C, 52.40; H, 5.39; N, 11.83%;
Found: C, 52.21; H, 5.34; N, 11.83%

Compound 139



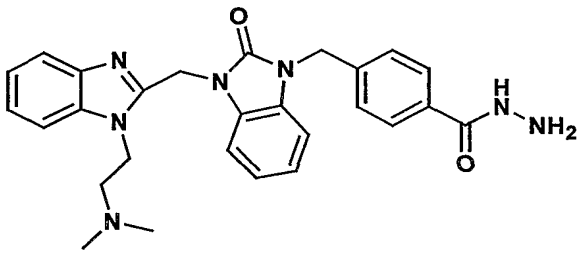
139

Compound **139** was prepared by the same procedure as compound **138** using N-methylpiperazine and acid **133**:

^{1}HNMR (CD_3OD) δ 2.92 (s, 3H), 3.06 (s, 6H), 3.65 (t, J = 8.0 Hz, 2H), 4.92 (t, J = 7.9 Hz, 2H), 5.22 (s, 2H), 5.54 (s, 2H), 7.09-7.14 (m, 3H), 7.34 (t, J = 8.0 Hz, 1H), 7.39-7.47 (m, 6H), 7.66-7.68 (m, 2H);
MS m/e 552 (MH^+);
IR (KBr, cm^{-1}) 3442, 1685, 1638, 1494, 1412, 1202, 1131;

Anal. Calcd for $C_{32}H_{37}N_7O_2 \bullet 3TFA \bullet 2.5H_2O$: C, 48.62; H, 4.83; N, 10.44
Found: C, 48.51; H, 4.44; N, 10.21.

Compound 140



A solution of the methyl ester **126** (484 mg, 1.0 mmol) and hydrazine (250 mg, 5.0 mmol) in MeOH (5 ml) was heated in a sealed tube at 90 °C for 4 h. After cooling, the precipitate formed was collected and washed with cold MeOH and dried to yield compound **140** (84 mg, 17%) as a white solid.

^{1}H NMR (CD_3OD) δ 3.08 (s, 6H), 3.71-3.78 (m, 2H), 5.01-5.08 (m, 2H), 5.17 (s, 2H), 5.68 (s, 2H), 7.06-7.19 (m, 3H), 7.42-7.57 (m, 5H), 7.70-7.73 (m, 1H), 7.85-7.91 (m, 3H);
MS m/e 484 (MH^+).

Compound 141

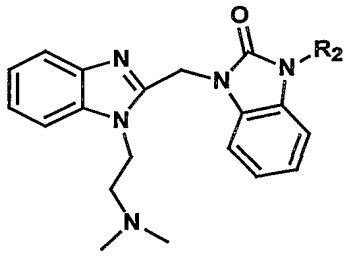
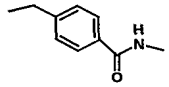
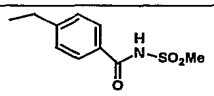
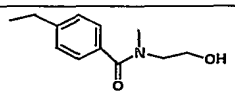
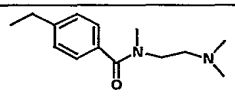
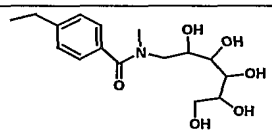
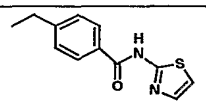
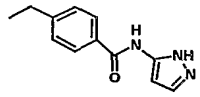
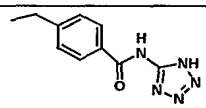
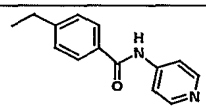
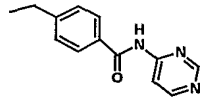
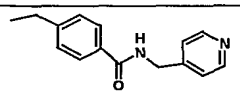
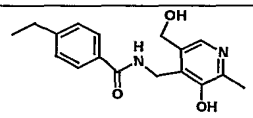


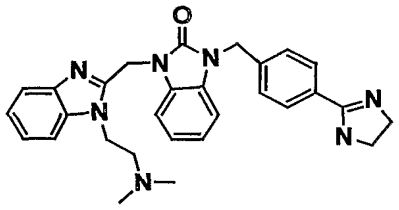
Table 13A - Compounds were prepared as described for compound **138** using acid **133** and a commercially available amine.

#	R_2	^{1}H-NMR Data	MS Data
141a		(DMSO-d6) δ 2.76 (d, J = 4.6Hz, 3H), 2.95 (s, 6H), 3.56-3.59 (m, 2H), 4.80 (t, J = 7.8Hz, 2H), 5.18 (s, 2H), 5,52 (s, 2H), 7.02-7.08 (m, 2H), 7.14-7.16 (m, 1H), 7.24-7.27 (m, 1H), 7.32-7.35 (m, 1H), 7.41 (d, J = 8.4Hz, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.2Hz, 1H), 7.78-7.80 (m, 2H), 8.39-8.41 (m, 1H), 9.99 (b, 1H)	483 (MH+)

141b		(CD3OD) δ 3.09 (s, 6H), 3.80-3.84 (m, 5H), 5.16-5.26 (m, 4H), 5.82 (s, 2H), 7.05-7.13 (m, 3H), 7.38-7.42 (m, 3H), 7.53-7.618 (m, 2H), 7.72-7.78 (m, 1H), 7.91-7.99 (m, 3H)	547 (MH+)
141c		(CD_3OD) δ 3.03-3.13 (m, 9H), 3.38-3.91 (m, 6H), 5.24-5.29 (m, 4H), 5.97 (s, 2H), 7.16-7.26 (m, 3H), 7.44-7.52 (m, 5H), 7.67-7.80 (m, 3H), 8.19 (d, J = 8.2Hz, 1H)	527 (MH+)
141d		(CD_3OD) δ 2.99 (s, 6H), 3.12 (s, 6H), 3.40 (t, J = 9.6Hz, 2H), 3.74-3.79 (m, 2H), 3.88 (t, J = 8.0 Hz, 2H), 5.21-5.27 (m, 4H), 5.97 (s, 2H), 7.15-7.25 (m, 3H), 7.49-7.54 (m, 3H), 7.67-7.82 (m, 3H), 7.91 (d, J = 8.3Hz, 2H), 8.17 (d, J = 8.3Hz, 1H)	540 (MH+)
141e		(CD_3OD) δ 3.06-3.14 (m, 9H), 3.47-3.88 (m, 10H), 5.21-5.28 (m, 4H), 5.95-5.98 (m, 2H), 7.20-7.22 (m, 3H), 7.44-7.52 (m, 5H), 7.66-7.80 (m, 3H), 8.17 (d, J = 8.2Hz, 1H)	647 (MH+)
141f		(CD_3OD) δ 3.10 (s, 6H), 3.88 (t, J = 7.9Hz, 2H), 5.24 (t, J = 7.9Hz, 2H), 5.31 (s, 2H), 5.97 (s, 2H), 7.17-7.24 (m, 3H), 7.44 (d, J = 4.0 Hz, 1H), 7.49 (d, J = 7.3Hz, 1H), 7.62 (d, J = 8.3Hz, 2H), 7.68-7.80 (m, 4H), 8.07 (d, J = 8.3Hz, 2H), 8.16 (d, J = 8.3Hz, 2H)	552 (MH+)
141g		(CD_3OD) δ 1.75 (s, 6H), 2.24 (t, J = 7.8Hz, 2H), 3.58 (t, J = 7.5Hz, 2H), 3.72 (s, 2H), 4.26 (s, 2H), 5.60-5.64 (m, 4H), 5.91 (d, J = 7.5Hz, 2H), 5.98 (d, J = 8.0 Hz, 2H), 6.00-6.06 (m, 1H), 6.06-6.13 (m, 1H), 6.19 (d, J = 8.0 Hz, 1H), 6.40-6.46 (m, 3H)	535 (MH+)
141h		(DMSO-d6) δ 2.35 (s, 6H), 2.74 (t, J = 6.2Hz, 2H), 4.52 (t, J = 6.4Hz, 2H), 5.23 (s, 2H), 5.76 (s, 2H), 7.01-7.04 (m, 2H), 7.14-7.27 (m, 4H), 7.52 (d, J = 8.1Hz, 2H), 7.57 (d, J = 8.6Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H)	537 (MH+)
141i		(CD_3OD) δ 3.10 (s, 6H), 3.84 (t, J = 8.2Hz, 2H), 5.18 (t, J = 7.9Hz, 2H), 5.30 (s, 2H), 5.90 (s, 2H), 7.15-7.22 (m, 3H), 7.48 (d, J = 7.6Hz, 1H), 7.59 (d, J = 8.9Hz, 2H), 7.63 (t, J = 7.3Hz, 1H), 7.69 (t, J = 7.3Hz, 1H), 7.77 (d, J = 8.2Hz, 1H), 8.04 (d, J = 8.9Hz, 2H), 8.07 (d, J = 8.2Hz, 1H), 8.39 (d, J = 7.6Hz, 2H), 8.66 (d, J = 7.6Hz, 2H)	546 (MH+)
141j		(CD_3OD) δ 2.29 (s, 6H), 2.64 (t, J = 6.9Hz, 2H), 4.51 (t, J = 6.9Hz, 2H), 5.27 (s, 2H), 5.53 (s, 2H), 7.04-7.07 (m, 3H), 7.22-7.34 (m, 3H), 7.52-7.55 (m, 3H), 7.96 (d, J = 8.3Hz, 2H), 8.32 (dd, J = 1.1, 5.8Hz, 1H), 8.64 (d, J = 5.9Hz, 1H), 8.86 (s, 1H)	547 (MH+)

141k		(CD_3OD) δ 3.04 (s, 6H), 3.74-3.79 (m, 2H), 5.08-5.13 (m, 2H), 5.21 (s, 2H), 5.81 (s, 2H), 7.08-7.15 (m, 4H), 7.40 (d, J = 6.6Hz, 1H), 7.47 (d, J = 8.4Hz, 1H), 7.53-7.64 (m, 2H), 7.70 (d, J = 8.1Hz, 1H), 7.86 (d, J = 8.4Hz, 2H), 7.98 (d, J = 6.6Hz, 3H), 8.73 (d, J = 6.9Hz, 2H)	561 (MH+)
141l		(CD_3OD) δ 2.65 (s, 3H), 3.08 (s, 6H), 3.67-3.85 (m, 2H), 4.70 (s, 2H), 4.96 (s, 2H), 5.14-5.19 (m, 2H), 5.24 (s, 2H), 5.87 (s, 2H), 7.10-7.19 (m, 3H), 7.45-7.50 (m, 3H), 7.60-7.64 (m, 2H), 7.75 (d, J = 7.8Hz, 1H), 7.88 (d, J = 8.4Hz, 2H), 8.08 (d, J = 8.1Hz, 1H), 8.18 (s, 1H)	620 (MH+)

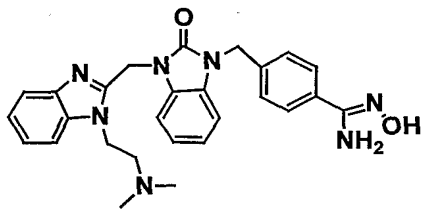
Compound 142



Carbon disulfide (0.5 mL) was added dropwise to ethylenediamine (5 g, 83.20 mmol). To this solution was added the nitrile (0.55 g, 1.22 mmol) and the resulting solution was stirred at 110 °C for 4 hours (Pharmazie, 1992, (47), 11-14). The excess ethylenediamine was evaporated and the residue was purified by preparative HPLC to compound **142**:

^1H NMR (CD_3OD) δ 3.09 (s, 6H), 3.77 (t, J = 7.9Hz, 2H), 4.08 (s, 4H), 5.09 (t, J = 7.7Hz, 2H), 5.29 (s, 2H), 5.75 (s, 2H), 7.07-7.18 (m, 3H), 7.42 (d, J = 7.7Hz, 1H), 7.51 (t, J = 7.6Hz, 1H), 7.57 (t, J = 7.8Hz, 1H), 7.61 (d, J = 7.9Hz, 2H), 7.72 (d, J = 8.1Hz, 1H), 7.85 (d, J = 8.2Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H)
MS m/e 494 (MH^+);

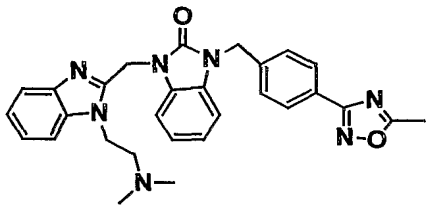
Compound 143



A mixture of compound **91m** (840 mg, 1.87 mmol), hydroxylamine hydrochloride (195 mg, 2.80 mmol) and triethylamine (321 mg, 3.18 mmol) in ethanol (20 ml) was heated to reflux for 12 h. After cooling, the product precipitated and was collected by filtration. The cake was washed with H_2O and cold MeOH. After drying, 610 mg (67%) of compound **143** was obtained as a white solid.

^{1}H NMR (CD_3OD) δ 3.11-3.12 (m, 6H), 3.89-3.93 (m, 2H), 5.22-5.25 (m, 2H), 5.30 (s, 2H), 5.98 (s, 2H), 7.13-7.24 (m, 4H), 7.51-7.54 (m, 2H), 7.61-7.79 (m, 5H), 8.17-8.19 (m, 1H);
MS m/e 413 (MH^+).

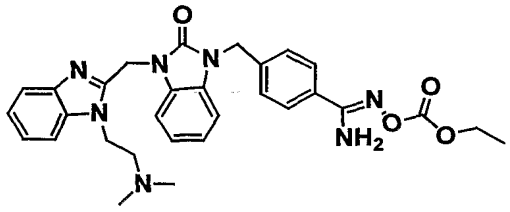
Compound 144



A solution of compound **143** (48 mg, 0.10 mmol) in Ac_2O (1 ml) was heated to 120°C for 4 h. The solvent was evaporated and the residue purified by prep-HPLC to yield 45 mg (88%) of compound **144** as a white solid.

^{1}H NMR ($CDCl_3$) δ 3.07 (s, 9H), 3.79 (t, J = 7.6Hz, 2H), 5.08 (t, J = 7.9Hz, 2H), 5.19 (s, 2H), 5.74 (s, 2H), 7.10-7.18 (m, 3H), 7.40-7.58 (m, 5H), 7.74 (d, J = 7.5Hz, 1H), 7.89-7.99 (m, 3H);
MS m/e 508 (MH^+).

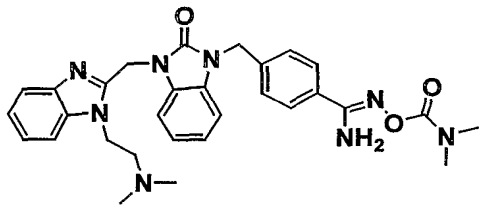
Compound 145



To a suspension of compound **143** (976 mg, 2.0 mmol), TEA (404 mg, 5.0 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (100 ml) was added ethyl chloroformate (259 mg, 2.4 mmol). After stirring for 12 h, the solution was concentrated and the residue purified by preparative reverse phase HPLC to yield 980 mg (88%) of compound **145** as a white solid.

^{1}H NMR (DMSO-d6) δ 1.25 (t, J = 7.2Hz, 3H), 2.95 (s, 6H), 3.55-3.58 (m, 2H), 4.16-4.20 (m, 2H), 4.80 (t, J = 7.6Hz, 2H), 5.18 (s, 2H), 5.52 (s, 2H), 6.82 (b, 1H), 7.02-7.08 (m, 2H), 7.16-7.17 (m, 1H), 7.23-7.26 (m, 1H), 7.31-7.35 (m, 2H), 7.41 (d, J = 8.4Hz, 2H), 7.61-7.70 (m, 4H), 9.99 (b, 1H);
MS m/e 556 (MH^+).

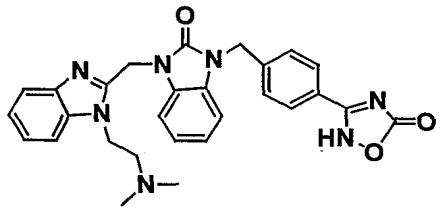
Compound 146



Compound **146** was prepared as described for compound **145** using N,N-dimethylcarbamoyl chloride.

^{1}H NMR (CD_3OD) 2.97-3.05 (m, 12H), 3.62-3.66 (m, 2H), 4.92-4.95 (m, 2H), 5.22 (s, 2H), 5.60 (s, 2H), 7.11-7.15 (m, 3H), 7.41-7.44 (m, 4H), 7.46-7.48 (m, 1H), 7.70-7.75 (m, 4H);
MS m/e 555 (MH^+).

Compound 147

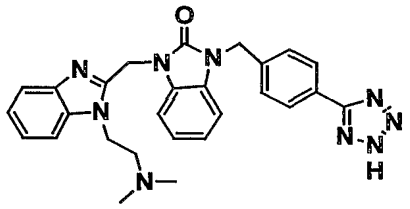


A solution of compound **145** (110 mg, 0.20 mmol) and DBU (110 mg, 0.74 mmol) in THF (10 ml) was heated to 80°C in sealed tube for 3h. Evaporated the

solvent. The residue was purified by prep-HPLC to yield 94 mg (92%) of compound **147** as a white solid.

^{1}H NMR (CD_3OD) δ 3.08 (s, 6H), 3.71-3.78 (m, 2H), 5.00-5.08 (m, 2H), 5.25 (s, 2H), 5.68 (s, 2H), 7.08-7.18 (m, 3H), 7.41-7.58 (m, 5H), 7.69-7.78 (m, 3H), 7.82 (d, J = 7.9Hz, 1H);
MS m/e 510 (MH^+).

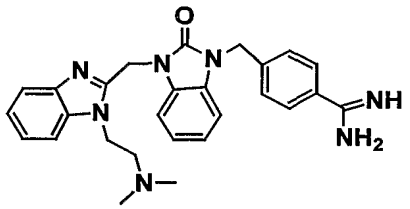
Compound 148



Compound **91m** was converted to the tetrazole as described for compound 52.

^{1}H NMR (CD_3OD) δ 3.13 (s, 6H), 3.87 (t, J = 8.0 Hz, 2H), 5.23 (t, J = 7.1Hz, 2H), 5.30 (s, 2H), 5.94 (s, 2H), 7.22-7.24 (m, 3H), 7.49-7.52 (m, 1H), 7.63 (d, J = 8.4Hz, 2H), 7.68-7.81 (m, 3H), 8.03 (d, J = 8.3Hz, 2H), 8.12-8.15 (m, 1H).

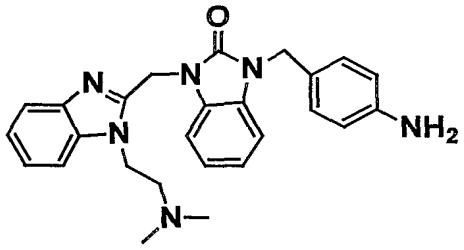
Compound 149



Compound **149** was prepared by hydrogenation of compound **146** as described for the hydrogenation of compound **115**.

^{1}H NMR (CD_3OD) δ 3.07 (s, 6H), 3.72 (t, J = 7.5Hz, 2H), 4.95-4.99 (m, 2H), 5.28 (s, 2H), 5.60 (s, 2H), 7.04-7.15 (m, 3H), 7.37-7.44 (m, 3H), 7.58-7.79 (m, 6H);
MS m/e 468 (MH^+).

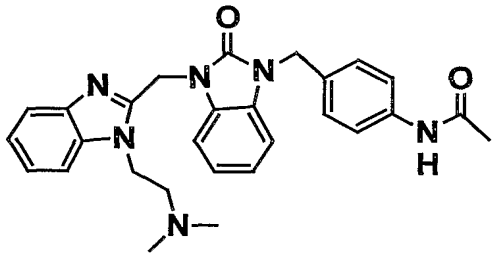
Compound 150



Compound **150** was prepared by catalytic hydrogenation of compound **91k** as described for compound **149** above.

^{1}H NMR (CD_3OD) δ 3.13 (s, 6H), 3.90 (t, J = 7.9 Hz, 2H), 5.21-5.26 (m, 4H), 5.97 (s, 2H), 7.16-7.26 (m, 3H), 7.42-7.52 (m, 3H), 7.61 (d, J = 8.5 Hz, 2H), 7.66-7.81 (m, 3H), 8.16 (d, J = 7.9 Hz, 2H);
MS m/e 441 (MH^+).

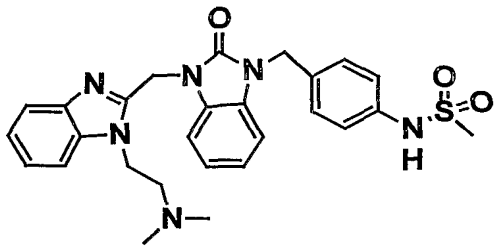
Compound 151



A mixture of compound **150** (100 mg, 0.18 mmol) and Et_3N (55 mg, 0.54 mmol) in methylene chloride (4 mL) was cooled to 0°C. Acetyl chloride (18 mg, 0.23 mmol) was added followed by DMAP (5 mg, catalytic quantity). The reaction mixture was allowed to warm to room temperature gradually and stirring was continued for 16 hours at room temperature under nitrogen atmosphere. A white precipitate was observed. The organic material was washed with dilute aqueous sodium bicarbonate solution (10 mL). The aqueous layer was then extracted with methylene chloride (2 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to give a white solid. The solid was triturated with anhydrous diethyl ether and filtered to give compound **151** as a white solid (50 mg, 53 % yield).

^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3 H), 3.36 (t, J = 6.9 Hz, 2 H), 4.25 (s, 3 H), 4.80 (t, J = 6.9 Hz, 2 H), 5.14 (s, 2 H), 5.34 (s, 2 H), 6.97-7.02 (m, 2 H), 7.07-7.23 (m, 6 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.48-7.54 (m, 4 H), 9.92 (s, 1H);
IR (KBr, cm^{-1}): 3308, 2929, 1694, 1610, 1516, 1495, 1407, 1311, 749.
MS m/e 522 (MH^+).
Anal. Calcd for $C_{28}H_{27}N_9O_2$: C, 64.48; H, 5.22; N, 24.17
Found: C, 64.13; H, 5.32; N, 23.86.

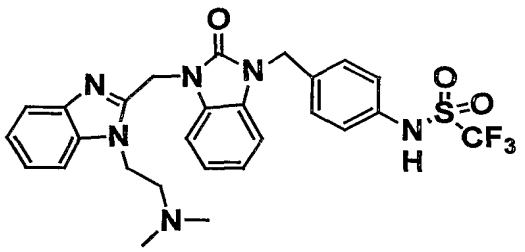
Compound 152



A mixture of compound **150** (100 mg, 0.18 mmol) and Et_3N (55 mg, 0.54 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. Methanesulfonyl chloride (21 mg, 0.18 mmol) was added and the reaction mixture was allowed to warm gradually to room temperature. After stirring for 5.5 h under nitrogen atmosphere, the organic material was washed with dilute aqueous sodium bicarbonate solution (10 mL). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Trituration with anhydrous diethyl ether followed by filtration gave compound **152** as a yellow solid (92 mg, 91% yield).

^{1}H NMR (CD_3OD) δ 2.95 (s, 3 H), 3.07 (s, 1H), 3.68 (t, J = 6.5 Hz, 2H), 4.26 (s, 3H), 5.14 (t, J = 6.7 Hz, 2H), 5.15 (s, 2H), 5.81 (s, 2H), 7.16-7.28 (m, 6H), 7.43 (d, J = 8.6 Hz, 2H), 7.63-7.75 (m, 3H), 7.99-8.02 (m, 1H);
IR (KBr, cm^{-1}): 3435, 2929, 1708, 1615, 1513, 1493, 1404, 1329, 1152, 752;
MS m/e 558 (MH^+).

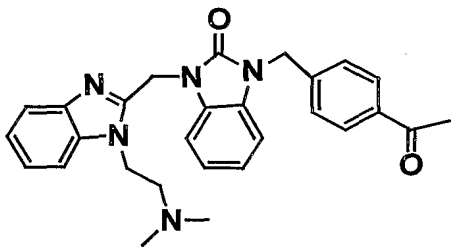
Compound 153



To a solution of compound **150** (600 mg, 1.36 mmol) and Et_3N (413 mg, 4.08 mmol) in CH_2Cl_2 (10 ml) at 0°C was triflic anhydride (460 mg, 1.63 mmol) dropwise. The solution was warmed to room temperature and stirred for 12 h, washed with sat. NH_4Cl, dried, evaporated, and purified by preparative reverse phase HPLC to yield compound **153** (522 mg, 67%) as white solid.

^1H NMR (CD_3OD) δ 3.11 (s, 6H), 3.85 (t, J = 8.1 Hz, 2H), 5.18-5.23 (m, 4H), 5.89 (s, 2H), 7.20-7.29 (m, 5H), 7.43-7.50 (m, 3H), 7.67-7.79 (m, 3H), 8.12 (d, J = 8.0 Hz, 1H);
MS m/e 573 (MH^+).

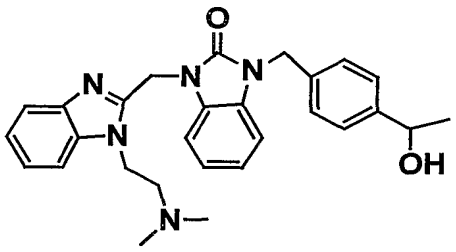
Compound 154



A mixture of compound **91m** (50 mg, 0.1 mmol), ethoxyvinyltributyltin (50 mg, 0.12 mmol) and palladium tetrakis(triphenylphosphine) (12 mg, 0.01 mmol) in toluene (1 ml) was heated to reflux under nitrogen. Diluted with CH_2Cl_2 (20 ml) and washed with sat. $NaHCO_3$, dried and concentrated. The residue was purified by prep-HPLC to yield 35 mg (67%) of compound **154** as a white solid.

^1H NMR (CD_3OD) δ 2.55 (s, 3H), 3.06 (s, 6H), 3.76 (t, J = 7.5Hz, 2H), 5.02 (t, J = 7.5Hz, 2H), 5.23 (s, 2H), 5.67 (s, 2H), 7.07-7.18 (m, 3H), 7.41-7.57 (m, 5H), 7.72 (d, J = 7.4Hz, 1H), 7.81-7.83 (m, 1H), 7.96 (d, J = 8.0 Hz, 2H);
MS m/e 468 (MH^+).

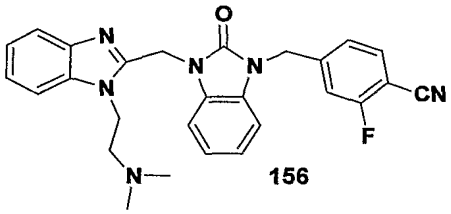
Compound 155



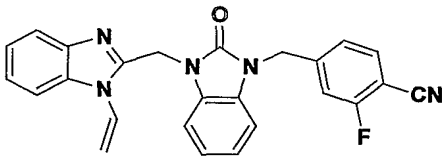
To a solution of compound **154** (24 mg, 0.05 mmol) in ethanol was added $NaBH_4$ (14 mg, 0.37 mmol) at 0°C. After stirring at this temperature for 30 min, the reaction mixture was quenched with 1 M HCl then extracted with EtOAc. The organic layer was washed with sat. $NaHCO_3$, dried, and concentrated. The residue was purified by preparative HPLC to yield 18 mg (75%) of compound **155** as a white solid.

^1H NMR (CD_3OD) δ 1.38 (d, J = 6.6Hz, 3H), 3.03 (s, 6H), 3.67 (t, J = 7.8Hz, 2H), 4.77-4.80 (m, 1H), 5.01 (t, J = 7.5Hz, 2H), 5.14 (s, 2H), 5.64 (s, 2H), 7.11-7.14 (m, 3H), 7.32-7.55 (m, 7H), 7.72 (d, J = 7.2Hz, 1H), 7.81 (d, J = 7.5Hz, 1H); MS m/e 470 (MH^+).

Compounds 156 and 157



156



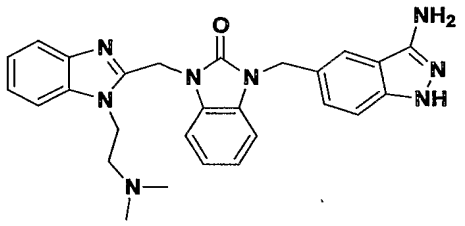
157

A mixture of 2-fluoro-4-methylbenzonitrile (5.0 g, 37 mmol), N-bromosuccinimide (6.4 g, 37 mmol) and AIBN (100 mg) was heated to reflux in CCl_4 (50 ml) for 12 h. The mixture was filtered and concentrated to give a 3:2 mixture of 2-fluoro-4-bromomethylbenzonitrile and starting material. A mixture of compound **128** (1.0 g, 2.98 mmol) and 2-fluoro-4-bromomethylbenzonitrile (0.91, 2.98 mmol) and Cs_2CO_3 (0.97 g, 2.98 mmol) in CH_3CN (50 ml) was heated to reflux for 30 minutes. The mixture was cooled, filtered and concentrated. The residue was purified by column chromatography (EtOAc to 3% MeOH/EtOAc as eluant) to give

(10 mg, 1%) of the first eluting vinyl compound **157** and (432 mg, 31%) of compound **156** product.

^{1}H NMR (DMSO-d6): δ 2.20 (s, 6H), 2.49-2.55 (m, 2H), 4.44 (t, J = 5.7 Hz, 2H), 5.18 (s, 2H), 5.45 (s, 2H), 7.01-7.14 (m, 2H), 7.16-7.25 (m, 5H), 7.51-7.58 (m, 4H), 7.77-7.81 (m, 1H), 7.92-7.95 (m, 1H);
MS m/e 468 (MH^+).

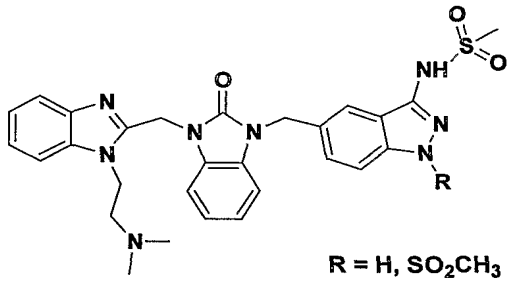
Compound 158



A mixture of compound **156** (210 mg, 0.45 mmol) and hydrazine (14 ml, 0.45 mmol) was heated to reflux in butanol for 12 h as described by R. F. Kaltenbach III, R. M. Klabe, B. C. Cordova and S. P. Seitz in *Biorg. Med. Chem. Lett.* **1999**, *15*, 2259-2262. The reaction was incomplete as judged by thin layer chromatography. Additional hydrazine (0.2 ml) was added and stirring continued at reflux for 12 h. The solvent was removed and the residue purified by flash column chromatography (3% MeOH/CH_2Cl_2 to 3% MeOH/CH_2Cl_2/0.1% NH_4OH to give compound **158** (200 mg, 92%) as a white solid.

^{1}H NMR (DMSO-d6) δ 2.19 (s, 6 H), 4.41-4.52 (m, 2 H), 5.13 (s, 2 H), 5.21-5.40 (m, 2 H), 5.45 (s, 2 H), 5.76 (s, 1 H), 6.95-7.08 (m, 2 H), 7.10-7.31 (m, 6 H), 7.52-7.59 (m, 2 H), 7.72 (s, 1 H), 11.40 (s, 1 H);
MS m/e 480 (MH^+).

Compounds 159 and 160



Compound **158** was treated with methanesulfonyl chloride as described for compound **152** to give a mixture of monomethanesulfonamide compound 160 and dimethanesulfonamide compound 159.

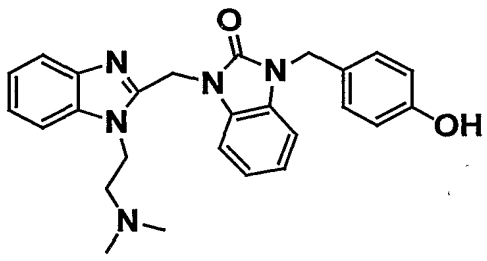
Compound 159; R = H:

^{1}H NMR (DMSO-d6) δ 2.33 (s, 6H), 3.36 (s, 3H), 3.50-3.60 (m, 2H), 4.84-4.90 (m, 2H), 5.27 (s, 2H), 5.57 (s, 3H), 7.00-7.15 (m, 2H), 7.18-7.25 (m, 2H), 7.25-7.40 (m, 2H), 7.40-7.50 (m, 3H), 7.59-7.65 (m, 1H), 7.78-7.81 (m, 2H);
MS m/e 558 (MH^+).

Compound 160; R = Ms

(DMSO-d6) δ 2.96 (s, 6H), 3.32 (s, 3H), 3.36 (s, 3H), 3.25-3.65 (m, 2H), 4.80-4.95 (m, 2H), 5.27 (s, 2H), 5.55 (s, 2H), 7.00-7.18 (m, 2H), 7.19-7.40 (m, 3H), 7.60-7.65 (m, 2H), 7.65-7.78 (m, 2H), 7.85-7.95 (m, 1H), 8.01 (s, 1H);
MS m/e 636 (MH^+).

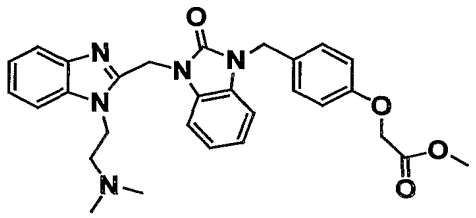
Compound 162



A mixture compound **91n** (600 mg, 1.05 mmol) and 10% palladium hydroxide on carbon (160 mg) in 2:1 MeOH/ THF (50 mL / 25 mL) was agitated under hydrogen at 55 psi for 48 hours. The reaction mixture was filtered through a pad of Celite and then subjected to column chromatography (2:1 EtOAc/CH_2Cl_2) to give compound **162** as a white solid (262 mg, 52% yield).

^{1}H NMR (DMSO-d_6) δ 3.35 (t, J = 6.8 Hz, 2H), 4.25 (s, 3H), 4.80 (t, J = 6.8 Hz, 2H), 4.94 (s, 2H), 5.33 (s, 2H), 6.68 (d, J = 8.5 Hz, 2H), 6.95-7.02 (m, 2H), 7.09-7.23 (m, 6H), 7.47-7.54 (m, 2H), 9.39 (s, 1H);
IR (KBr, cm^{-1}) 3247, 2944, 1664, 1613, 1597, 1515, 1491, 1445, 1413, 747;
MS m/e 481 (MH^+);
Anal. Calcd for $C_{26}H_{24}N_8O_2$: C, 64.99; H, 5.03; N, 23.32
Found: C, 64.79; H, 4.98; N, 23.38.

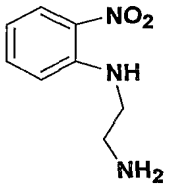
Compound 163



To the compound **162** (127 mg, 0.26 mmol) DMF (5 mL) was added NaH (60% suspension in mineral oil, 13 mg, 0.32 mmol) while stirring under nitrogen atmosphere. After stirring for 15 minutes, methyl bromoacetate (48 mg, 0.32 mmol) was added. The reaction was stirred at room temperature for 16 hours. Column chromatography on silica gel (gradient, CH_2Cl_2 to 1% MeOH in CH_2Cl_2) gave compound **163** as a solid (142 mg, 97% yield).

^{1}H NMR (DMSO-d_6) δ 3.36 (t, *J* = 6.7 Hz, 2 H), 3.66 (s, 3 H), 4.25 (s, 3H), 4.74 (s, 3H), 4.80 (t, *J* = 6.9 Hz, 2 H), 5.00 (s, 2 H), 5.33 (s, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.98-7.01 (m, 2 H), 7.13-7.23 (m, 4 H), 7.30 (d, *J* = 8.7 Hz, 2 H), 7.51 (dd, *J* = 12.9, 7.4 Hz, 2 H);
IR (KBr, cm^{-1}): 2922, 1745, 1698, 1611, 1509, 1498, 1438, 1230, 742.
MS m/e 553 (MH^+).
Anal. Calcd for $C_{29}H_{28}N_8O_4$: C, 63.03; H, 5.11; N, 20.28
Found: C, 63.20; H, 5.14; N, 18.48

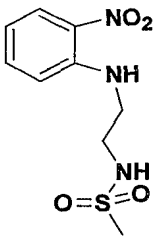
Compound 164



A solution of 2-fluoronitrobenzene (30 mL, 2.84 mmol) in acetonitrile (30 mL) was added to a solution of ethylenediamine (76 mL, 1.14 mmol) in acetonitrile (50 mL). The mixture was stirred at room temperature for 12 h then concentrated to give 51 g (99% yield) of compound **164** as an orange oil.

^{1}H NMR (DMSO-d_6) δ 2.82 (t, J = 6.0 Hz, 2 H), 3.30 (t, J = 6.0 Hz, 2 H), 6.66 (t, J = 8.4 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 8.30-8.34 (m, 1 H);
IR (film, cm^{-1}) 1621, 1514, 1347, 740;
MS m/e 182 (MH^+);
Anal. Calcd for $C_8H_{11}N_3O_2 \cdot 0.20\ H_2O$: C, 51.99; H, 6.22; N, 22.74
Found: C, 51.99; H, 6.29; N, 22.46.

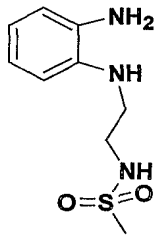
Compound 165



To a mixture of amine **164** (2.0 g, 11 mmol) in CH_2Cl_2 (50 mL) was added triethyl amine (1.53 mL, 11 mol) and the mixture was cooled to 0°C. Methanesulfonyl chloride (0.85 mL, 11 mmol) was added slowly. Once the addition was complete, the reaction mixture was warmed to room temperature and stirred for 12h. The mixture was poured into water and the aqueous layer separated, dried over $MgSO_4$, and evaporated. The residue was chromatographed with 3% methanol in dichloromethane to give 2.55 g (89%) of compound **165** as an orange oil:

^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3H), 3.18 (dd, J = 6.1, 11.6 Hz, 2H), 3.39-3.42 (m, 2H), 6.70 (t, J = 9.0 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.28 (t, J = 6.1 Hz, exchanges with D_2O, 1H), 7.55 (td, J = 1.0, 6.0, Hz, 1H); 8.07 (dd, J = 1.0, 8.7 Hz, 1H); 8.23 (br s, 1H exchanges with D_2O);
IR (film, cm^{-1}) 1511, 1354, 1317, 1151;
MS m/e 260 (MH^+);
Anal. Calcd for $C_9H_{13}N_3O_4S \cdot 0.5\ H_2O \cdot 0.08$ EtOAc:
C, 40.66; H, 5.36; N, 15.26.
Found: C,40.58; H, 5.29; N, 14.88.

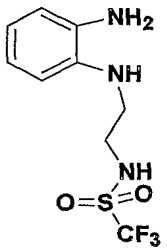
Compound 166



A mixture of compound **165** (1.0 g, 3.9 mmol) and 10% Pd/C (100 mg) in ethanol (50 mL) was hydrogenated at 50 psi for 12 h. The mixture was filtered and the filtrate was evaporated to give an orange oil. The residue was chromatographed (1% MeOH in CH_2Cl_2) to give 0.55g (62% yield) of compound **166** as a dark oil:

^{1}H NMR (DMSO-d_6) δ 2.91 (s, 3H), 3.17 (br s, 2H), 4.45 (br s, 3H, 1H exchanges with D_2O), 6.40-6.56 (m, 4H), 7.11 (br s, 1H, exchanges with D_2O);
IR (film, cm^{-1}) 3326, 1625, 1510, 1315, 1148, 738;
MS m/e 230 (MH^+);
Anal. Calcd for $C_9H_{15}N_3O_2S$: C, 46.78; H, 6.63; N, 18.18
Found: C, 46.81 ; H, 6.79; N, 17.81.

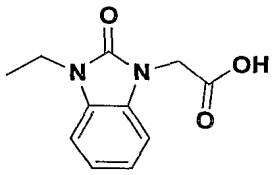
Compound 167



Compound **167** was prepared as described for **166** above.

^{1}H NMR (DMSO-d_6) δ 3.17-3.21 (m, 2H), 3.31-3.35 (m, 4H, 2H exchange with D_2O), 6.42-6.57 (m, 4H);
IR (film, cm^{-1}) 1365, 1143;
MS m/e 283 (MH^+).

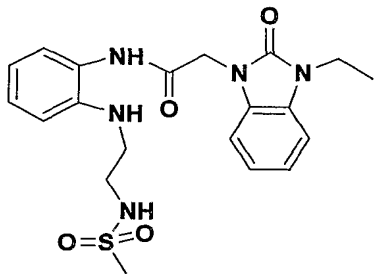
Compound 168



A mixture of 1,3 dihydro-2-H-1-ethylbenzimidazol-2-one (5.0 g, 30.8 mmol), ethyl bromoacetate (3.4 mL, 30.8 mmol) and potassium carbonate (4.25 g, 30.8 mmol) in acetonitrile (50 mL) was heated to reflux for 12h, and then evaporated. To the residue was added 6 N HCl (100 mL) and the resulting mixture was heated to reflux for 4 h. The solution was cooled to room temperature and precipitate was filtered to give 6.2 g (99% yield) of compound **168** as white needles: mp 225-227°C;

^{1}H NMR (DMSO-d_6) δ 1.20 (t, J = 7.1 Hz, 3H), 3.87 (q, J = 7.1, 14.1 Hz, 2H), 4.60 (s, 2H), 7.00-7.10 (m, 2H), 7.13-7.16 (m, 1H), 7.21-7.24 (m, 2H);
IR (KBr, cm^{-1}) 3000, 1750, 1655, 752;
MS m/e 230 (MH^+);
Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72.
Found: C, 59.82 ; H, 5.43; N, 12.64.

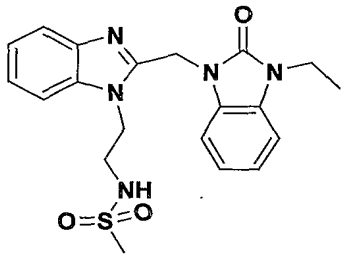
Compound 169



Acid **168** (0.48 g, 2.2 mmol) was refluxed with thionyl chloride (2 mL) for 30 minutes and then evaporated to dryness. To the residue was added a solution of diamine **166** (0.5 g, 2.2 mmol) and triethylamine (0.55 mL, 4.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 12 h and then poured into water. The organic layer was separated, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluted with 3% methanol in methylene chloride to give 810 mg (86% yield) of **169** as a light green solid: mp 82-85 °C;

^{1}H NMR (DMSO-d_6) δ 1.23 (t, J = 7.1 Hz, 3H), 2.90 (s, 3H), 3.13-3.17 (m, 2H), 3.18-24 (m, 2H), 3.90 (q, J = 7.1, 14.1 Hz, 2H), 4.71 (s, 2H), 5.18 (t, J = 7.1 Hz, 1H, exchanges with D_2O), 6.58 (t, J = 7.6 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 7.03-7.24 (m, 6H), 9.44 (s, 1H, exchanges with D_2O);
IR (KBr, cm^{-1}) 1686, 1522, 1317, 1149;
MS m/e 432 (MH^+).
Anal. Calcd for $C_{20}H_{25}N_5O_4 \cdot 0.3\ H_2O$: C, 54.98; H, 5.91; N, 16.03
Found: C,55.07 ; H, 5.97; N, 15.65.

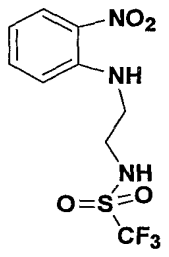
Compound 170



Amide **169** (0.72g, 1.67 mmol) was heated to reflux in acetic acid for 12 h and evaporated. The residue was purified by chromatography (3% MeOH in CH_2Cl_2) to give 0.37 g (53% yield) of compound **170** as a white solid: mp 57-60°C;

^{1}H NMR (DMSO-d_6) δ 1.24 (t, J = 7.1 Hz, 3H), 1.90 (s, 3H), 3.38-3.34 (m, 2H), 3.92 (q, J = 7.1, 14.7 Hz, 2H); 4.49 (t, J = 6.0 Hz, 2H); 5.41 (s, 2H); 6.98-7.28(m, 6H); 7.40 (t, J = 6.0, 1H, exchanged with D_2O), 7.54 (d, J = 7.7Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H);
IR (KBr cm^{-1}) 1693, 1317, 1140, 744;
MS m/e 414 (MH^+).
Anal. Calcd for $C_{20}H_{25}N_5O_4S \cdot 1.1\ H_2O$: C, 55.65; H, 5.76; N, 14.75.
Found: C, 55.65; H, 5.74; N, 14.72.

Compound 171



To a mixture of amine **164** (3.0 g, 13.8 mmol) in CH_2Cl_2 (50 mL) was added triethyl amine (3.8 mL, 28 mol) and the mixture was cooled to 0°C. Trifluoromethanesulfonic anhydride (2.32 mL, 13.8 mmol) was added slowly. Once the addition was complete the reaction mixture was warmed to room temperature and stirred for 12h. The mixture was poured into water and the aqueous layer separated, dried over $MgSO_4$, and evaporated. The residue was was dissolved in MeOH and treated with 25% NaOH (1 mL) and stirred for 6h. The mixture is acidified and

extracted with EtOAc. The organic layer was dried and concentrated to give 1.07 g (71%) of compound **171**.

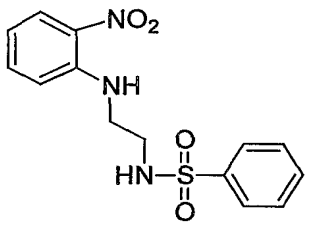
1H NMR (DMSO-d6) d 3.38 (t, J = 5.8 Hz, 2H), 3.52-3.58 (m, 2H), 6.72 (t, J = 6.8 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 7.55 (t, J = 7.1 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 8.22 (t, J = 3.06 Hz, 1H, exchanges with D_2O)

MS m/e 313 (MH^+);

Anal. Calcd for $C_9H_{10}F_3N_3O_4S$: C, 34.51; H, 3.22; N, 13.41

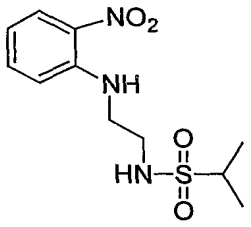
Found: C, 34.39 ; H, 3.20; N, 13.24.

Compound 172



To a solution of compound **164** (2 g, 9.2 mmol) in CH_2Cl_2 (70 ml) was added Triethylamine (2.32 g, 22.9 mmol) at 0°C. Benzenesulfonyl chloride(1.95 g, 11.04 mmol) was added slowly and the mixture was stirred overnight at room temperature. The mixture was diluted with CH_2Cl_2 and washed with water, 1N HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated to give 3.06 g (97% yield) of the compound **172** as a yellow solid.

Compound 173



To a solution of compound **164** (2 g, 9.2 mmol) in CH_2Cl_2 (70 ml) was added Triethylamine (2.32 g, 22.9 mmol) at 0 C. Isopropylsulfonyl chloride (1.57 g, 11.0 mmol) was added slowly and the mixture was stirred overnight at room temperature. The mixture was diluted with CH_2Cl_2 and washed with water, 1N HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated to give 830 mg (31% yield) of the compound **173** as a yellow oil.

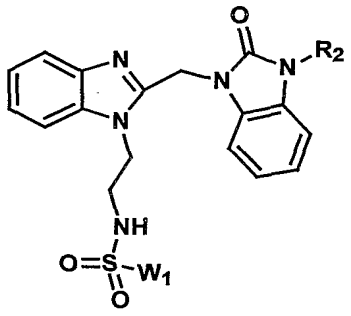


Table 14- Compounds were prepared as described for compound **170**.

#	R_2	W_1	^{1}H-NMR Data	MS Data
174a	CH_2CO_2Et	Me	(DMSO-d6) δ 1.20 (t, J = 7.1Hz, 3H), 2.81 (s, 3H), 3.25 (t, J = 5.9Hz, 2H), 4.07 (q, J = 7.1Hz, 2H), 4.39 (t, J = 5.8 Hz, 2H), 4.69 (s, 2H), 5.34 (s, 2H), 6.94-6.98 (m, 2H), 7.08-7.16 (m, 4H), 7.45 (d, J = 7.7Hz, 1H), 7.49 (d, J = 7.9Hz, 1H)	471 (MH+)
174b	CH_2CO_2Et	CF_3	(DMSO-d6) δ 1.22 (t, J = 6.3Hz, 3H), 3.51-3.62 (m, 2H), 4.17 (q, J = 7.2Hz, 2H), 4.45-4.58 (m, 2H), 4.76 (s, 2H), 5.43 (s, 2 H), 7.05-7.10 (m, 2H), 7.16-7.29 (m, 4H), 7.57 (d, J = 7.8Hz, 2H), 9.81 (s, 1H, exchanges with D_2O)	525 (MH+)
174c	CH_2CO_2Et	Ph	1H NMR (DMSO-d6) d 1.21 (t, *J* = 7.1, 3 H), 3.09-3.13 (m, 2 H), 4.15 (q, *J* = 7.1, 2 H), 4.45-4.4.67 (m, 2 H), 4.78 (s, 2 H), 5.43 (s, 2 H), 7.01-7.26 (m, 6 H), 7.50-7.65 (m, 5 H), 7.73 (d, *J* = 7.1, 2 H), 8.03 (t, *J* = 6.2, 1 H);	MS m/e 534 (MH+);

5

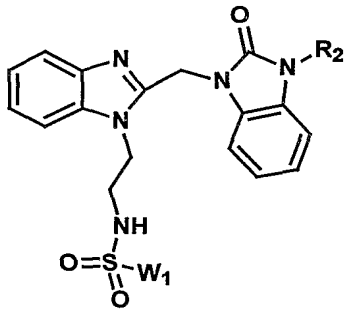
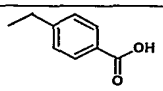
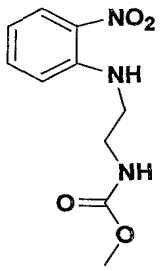


Table 15 - Prepared as described for compound **8**.

#	R_2	W_1	^{1}H-NMR Data	MS Data
175a	CH_2CO_2H	CF_3	(DMSO-d6) δ 3.48-3.60 (m, 2H), 4.43-4.58 (m, 2H), 4.67 (s, 2H), 5.41 (s, 2H), 7.03-7.10 (m, 2 H), 7.14-7.27 (m, 5H), 7.54 (d, J = 7.8 Hz, 2H)	497 (MH+)
175b	CH_2CO_2H	CH_3	(DMSO-d6 δ 2.78 (s, 3H), 3.32 (t, J = 5.2 Hz, 2H), 4.45 (t, J = 5.8Hz, 2H), 4.65 (s, 3H), 5.41 (s, 2H), 6.99-7.10 (m, 2 H), 7.10-7.22 (m, 4H), 7.52-7.58	443 (MH+)

			(m, 2H)	
175c		CH_3	(DMSO-d6) δ 2.84 (s, 3H), 6.38-6.46 (m, 2H), 4.55-4.61 (m, 2H), 5.60 (s, 2H), 5.76 (s, 2H), 7.02-7.06 (m, 2H), 7.14-7.16 (m, 1H), 7.27-7.31 (m, 2H), 7.36-7.39 (m, 1H), 7.44-7.46 (m, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.1 Hz, 2H)	520 (MH+)
175d	CH_2CO_2H	iPr	(DMSO-d6) d 1.11 (d, J = 6.8, 6 H), 1.22 (t, *J* = 7.1, 3 H), 3.07-3.16 (m, 2 H), 4.16 (q, *J* = 7.1, 2 H), 4.31-4.33 (m, 2 H), 4.78 (s, 2 H), 5.44 (s, 2 H), 7.00-7.08 (m, 2 H), 7.13-7.27 (m, 3 H), 7.35 (t, *J* = 6.3, 1 H), 7.53-7.59 (m, 2 H);	500 (MH+)

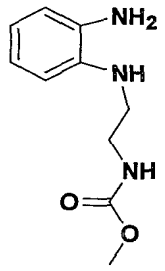
Compound 176



To a slurry of compound **164** (2.0 g, 9.2 mmol) and $KHCO_3$ (2.3 g, 23.0 mmol) was added methyl chloroformate (1.42 ml, 18.4 mmol) and the mixture stirred at 23°C for 12h. The reaction mixture is extracted with EtOAc. The organic extracts are combined, dried over $MgSO_4$ and concentrated to give 1.82 g (83%) of compound **176** as a yellow solid.

^{1}H NMR (DMSO-d_6) δ 3.19-3.25 (m, 2H), 3.39-3.45 (m, 2H), 3.52 (s, 3H), 6.67 (t, J = 7.3Hz, 1H), 7.12 (d, J = 8. 7Hz, 1H), 7.37 (br t, 1H, exchanges with D_2O), 7.53 (t, 7.2 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 8.20 (br t, 1H, exchanges with D_2O)
IR (film, cm^{-1}) 1736, 1515, 1353;
MS m/e 239 (MH^+);
Anal. Calcd for $C_{10}H_{135}N_3O_4$: C, 50.21; H, 5.48; N, 17.56
Found: C, 50.15 ; H, 5.61; N, 17.58.

Compound 177

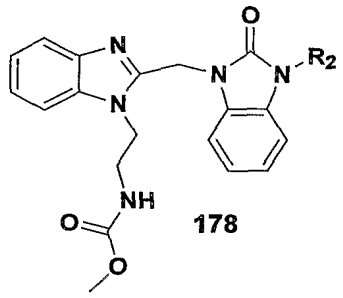


Compound **177** was prepared as described for compound **166** above.

^{1}H NMR (DMSO-d_6) δ 3.03-3.10 (m, 2H), 3.16-3.22 (m, 2H), 3.53 (s, 3H), 4.40-4.45 (m, 2H, exchanges with D_2O), 6.38-6.55 (m, 4H), 7.21 (t, J = 5.3 Hz, 1H, exchanges with D_2O);

IR (film, cm^{-1}) 1702, 1565, 733;

MS m/e 209 (MH^+).



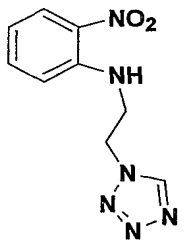
178

Table 16- Compounds were prepared as described for compound **170** using **177**.

#	R_2	^{1}H-NMR Data	MS Data
178a	Et	1H NMR (DMSO-d6) d 1.23 (t, *J* = 7.1, 3 H), 3.32-3.38 (m, 2 H), 3.47 (s, 3 H), 3.91 (q, *J* = 7.2, 2 H), 4.43 (t, *J* = 6.0, 2 H), 5.33 (s, 2 H), 6.97-7.09 (m, 2 H), 7.13-7.24 (m, 4H), 7.46-7.55 (m, 2H);	MS m/e 394 (MH+);
178b	CH_2CO_2Et	DMSO-d6: 1.22 (t, J = 7.10 Hz, 3H), 3.33 (s, 3H), 3.32-3.42 (m, 2H), 4.17 (q, J = 7.10 Hz, 2H), 4.40-4.48 (m, 2H), 4.79 (s, 2H), 5.37 (s, 2H), 7.01-7.16 (m, 2H), 7.21-29 (m, 3H), 7.32-7.39 (m, 1H), 7.55-7.65 (m, 2H)	451 (MH+)
178c[a]	CH_2CO_2H	(DMSO-d6) 3.25-3.34 (m, 2 H), 3.48 (s,3 H), 4.41-4.45 (m, 2 H), 4.68 (s, 2 H), 5.37 (s, 2 H), 7.03-7.10 (m, 2 H), 7.05-7.30 (m, 4 H), 7.30-7.38 (m, 2 H), 7.43-7.58 (m, 2 H)	423 (MH+)

a, ester hydrolyzed as described for compound **8**.

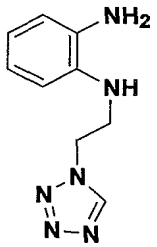
Compound 179



A mixture of amine **164** (40 g, 220 mmol), trimethyl ortho formate (38.5 mL, 352 mmol) and sodium azide (15.7 g, 242 mmol) in acetic acid (400 mL) was heated to reflux for 12 h. The resulting mixture was cooled to room temperature and poured into 1N HCl in ice (300 mL). The precipitate was filtered and recrystallized from ethyl acetate to give 19.2 g (37% yield) of compound **179** as bright yellow needles:

^{1}H NMR (DMSO-d_6) δ 3.90 (J = 6.6 Hz, 2H), 4.73 (t, J = 6.6 Hz, 2H), 6.72 (t, J = 6.9 Hz, 1H), 7.07 (d, J = 10.2 Hz, 1H), 7.53 (d, J = 6.3 Hz, 1H), 8.06 (d, J = 10.1 Hz, 1 H), 8.18 (t, J = 6.6 Hz, 1H); 9.40 (s, 1 H);
IR (KBr, cm^{-1}) 1621, 1514, 1347, 740;
MS m/e 235 (MH^+);
Anal. Calcd for $C_9H_{10}N_6O_2$: C, 46.15; H, 4.30; N, 35.88.
Found: C, 46.17; H, 4.35; N, 35.85.

Compound 180

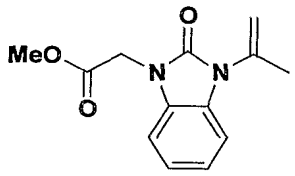


A solution of nitroaniline **179** (3.5 g, 14.95 mmol) in ethanol (50 mL) containing 10% Pd/C (200 mg) was hydrogenated at 50 psi for 4 h. The reaction mixture was filtered and concentrated to give 2.8 g (93% yield) of compound **180** as a black solid:

^{1}H NMR (DMSO-d_6) δ 3.52 (q, J = 6.0, 2H), 4.46 (s, 3H), 4.63-4.69 (m, 3H), 6.45-6.57 (m, 4H), 9.4 (s, 1H);

MS m/e 205 (MH^+).

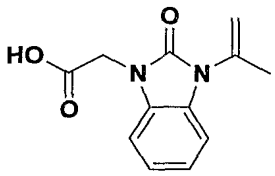
Compound 181



N-isopropenyl-2-benzimidazolone (15.0g, 86.10mmol), methyl bromoacetate (13.2 g, 86.1 mmol) and potassium carbonate (14.25g, 103.26 mmol) were stirred in acetonitrile (300ml) at room temperature overnight. The next day the reaction mixture was filtered and concentrated to give 21.0g (99% yield) of product **181** as a clear oil:

^1H NMR (DMSO) δ 2.13 (s, 3H), 3.69 (s, 3H), 4.74 (s, 2H), 5.17 (s, 1H), 5.38 (s, 1H), 7.05-7.23 (m, 4H);
IR (KBr, cm^{-1}) 2955, 1755, 1714, 1493, 757;
MS m/e 247 (MH^+).

Compound 182

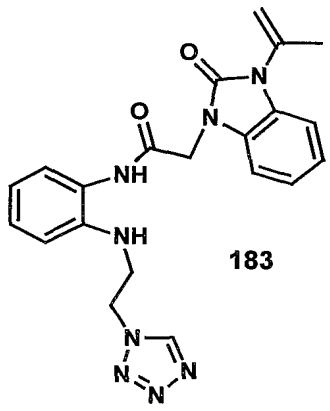


The solution of ester **181** (3.33g, 17.79mmol) in methanol (20 mL) was stirred with 1N NaOH (19.19ml, 19.18mmol) at room temperature overnight. The solvent was evaporated and the residue dissolved in water and acidified with 1N HCl. The precipitate was filtered off, washed with water and dried under vacuum to give 2.7g (91% yield) of compound **182** as a white solid:

^1H NMR (DMSO-d_6) δ 2.15 (s, 3H), 4.62 (s, 2H), 5.18 (s, 1H), 5.4 (s, 1H), 7.07-7.21 (m, 4H);
IR (KBr, cm^{-1}) 2967, 1751 1675, 1206, 752;
MS m/e 233 (MH^+);

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06
Found: C, 61.69; H, 5.33; N, 11.98

Compound 183

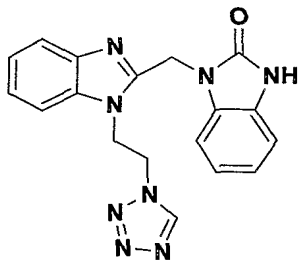


183

To a mixture of acid **182** (1.35g, 6.61mmol) and 2-chloro-1-methylpyridinium iodide (2.02g, 7.92mmol) in acetonitrile (30mL) was added triethylamine (3.21mL, 23.13 mmol), followed by diamine **180** (1.53g, 6.61mmol). The reaction mixture was stirred at room temperature overnight. The precipitate was filtered and dried under vacuum to give compound **183** (1.281g, 46% yield): mp 184-186 °C.

^{1}H NMR (DMSO-d_6) δ 2.15 (s, 3H), 3.59 (q, J = 6.5 Hz, 2H), 4.64 (t, J = 6.6 Hz, 2H), 4.71 (s, 2H), 5.17 (s, 1H), 5.36-5.39 (m, 2H), 6.60 (t, J = 7.5 Hz, 1H), 6.70 (d, J = 7.4 Hz, 2H), 7.02-7.19 (m, 6H), 9.34 (s, 1H), 9.48 (s, 1H);
IR (KBr, cm^{-1}) 3400, 1710, 1680, 1493, 1426, 742;
MS m/e 419 (MH^+);
Anal. Calcd for $C_{21}H_{22}N_8O_2$: C, 60.28; H, 5.30; N, 26.78
Found: C, 59.92; H, 5.31; N, 26.41.

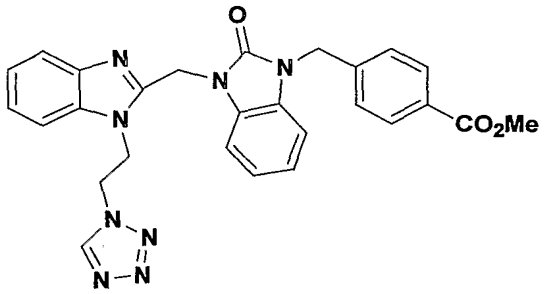
Compound 184



A solution of compound **183** (1.25g, 2.98mmol) in acetic acid (40 ml) was refluxed overnight. The solvent was evaporated to give compound **184** as an off-white solid (850mg, 79% yield): mp >200 °C

^{1}H NMR (DMSO-d_6) δ 4.91-4.98 (m, 4H), 5.14 (s, 2H), 6.95-7.0 (m, 3H), 7.10-7.17 (m, 3H), 7.25-7.27 (m, 1H), 7.50-7.54 (m, 1H), 9.28 (s, 1H), 11.03 (s, 1H);
IR (KBr, cm^{-1}) 3429, 3256, 1694, 1489, 738;
MS m/e 361 (MH^+);
Anal. Calcd for $C_{18}H_{16}N_8O \cdot 0.33\ H_2O \cdot 0.35$ EtOAc: C, 58.67; H, 4.94; N, 28.21
Found: C, 58.55; H, 4.69; N, 27.83

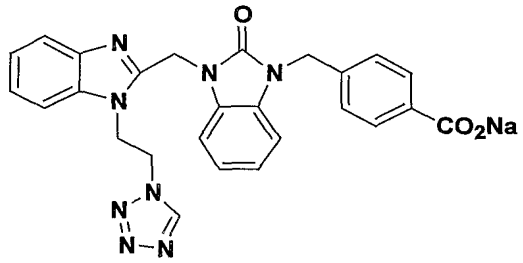
Compound 185



A mixture of compound **184** (1.0 g, 2.77 mmol) and Cs_2CO_3 (904 mg, 2.77 mmol) in CH_3CN (40mL) was heated to reflux for 10 minutes, and then methyl 4-(bromomethyl)benzoate (636mg, 2.77mmol) in CH_3CN (5 mL) was added. The resulting mixture was refluxed for 30 minutes and cooled to room temperature. The mixture was filtered and the filtrate was evaporated. Flash chromatography (MeOH:CH_2Cl_2 = 5:95) gave 700 mg (50% yield) of compound **185** as a white solid: mp 144-147 °C;

^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 4.94-5.01 (m, 4H), 5.21 (s, 2H), 5.27 (s, 2H), 6.7-7.07 (m, 2H), 7.11-7.19 (m, 3H), 7.22-7.31 (m, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.54-7.56 (m, 1H), 7.93 (d, J = 8.3 Hz, 2H), 9.31 (s, 1H);
IR (KBr, cm^{-1}) 3423, 1714, 1437, 1284, 1110, 748;
MS m/e 509 (MH^+);
HRMS calcd for $C_{27}H_{24}N_8O_3$, 509.2049; found, 509.2046

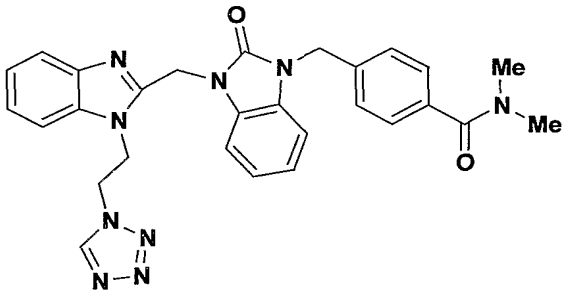
Compound 186



To a solution of compound **185** (1.82 g, 3.57 mmol) in methanol (110 mL) was added lithium hydroxide monohydrate (0.90g, 21.47mmol) in water (20 mL). The resulting mixture was stirred overnight at room temperature and evaporated. The residue was diluted with water and acidified with 1N HCl. The white precipitate was filtered and dried under vacuum. To the solid in methanol (120 mL) was added one equivalent of 0.5 M NaOMe (5.5 mL) at room temperature under nitrogen and the solution was stirred for 3 hours. The solvent was evaporated and dried under vacuum to give 1.38 g (74% yield) of compound **186** as a white solid:

^{1}H NMR (DMSO-d_6) δ 4.92-5.05 (m, 4H), 5.18 (s, 2H), 5.26 (s, 2H), 7.01-7.03 (m, 2H), 7.1-7.29 (m, 3H), 7.38-7.45 (m, 2H), 7.51-7.54 (m, 1H), 7.89 (d, J = 8.3, 4H), 9.29 (s, 1H);
IR (KBr, cm^{-1}) 3406, 1695, 1599,1556, 1396, 750;
MS m/e 495(MH^+).

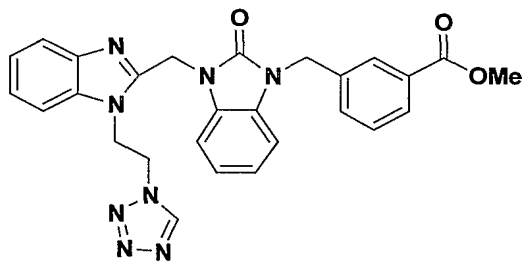
Compound 187



To a mixture of acid **186** (250 mg, 0.5 mmol), dimethylamine hydrochloride (62 mg, 0.75 mmol) and diisopropyl ethylamine (131 mg, 1.0 mmol) in DMF (10 mL) was added PyBroP (283 mg, 0.60 mmol) in one portion. The reaction was stirred at room temperature overnight, quenched with MeOH (1 mL), and evaporated. The residue was taken into ethyl acetate and washed with 5% $KHSO_4$, 5% $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated. The crude solid was washed with ethyl acetate and large portions of water to give181 mg (69% yield) of compound **187** as a white solid: mp >200 °C

^{1}H NMR (DMSO-d_6) δ 2.86 (s, 3H), 2.95 (s, 3H), 4.93-4.95 (m, 2H), 5.0-5.02 (m, 2 H), 5.15 (s, 2H), 5.26 (s, 2H), 7.02-7.04 (m, 2H), 7.14-7.17 (m, 3H), 7.23-7.24 (m, 1H), 7.28-7.3 (m, 1H), 7.38 (q, J = 5.0 Hz, 4H), 7.53 (d, J = 5.3 Hz, 1H), 9.31 (s, 1H); MS m/e 521(MH^+).

Compound 188

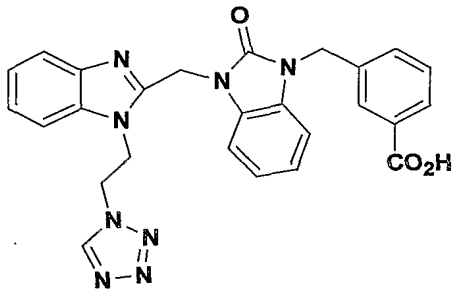


Compound **184** (300mg, 0.83mmol) in THF (5 mL) was added BTPP (0.51mL, 1.82mmol) under nitrogen at 0 °C. After stirring for 15 minutes, methyl 3-(bromomethyl)benzoate (190.7 mg, 0.83 mmol) was added. The reaction mixture was allowed to warm up to room temperature overnight under nitrogen and

evapoarted. The residue was diluted with water and extracted with ether and ethyl acetate. The combined extracts were dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_4OH = 90:10:1 to give 196mg (46% yield) of compound **188** as a white solid: mp 162-164 °C;

^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 4.92-5.05 (m, 4H), 5.19 (s, 2H), 5.27 (s, 2H), 6.99-7.05 (m, 2H), 7.11-7.17 (m, 3H), 7.20-7.28 (m, 2H), 7.48-7.55(m, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 6.5 Hz, 1H), 7.97 (s, 1 H), 9.29 (s, 1H);
IR (KBr, cm^{-1}) 3424, 1701, 1494, 1434, 1289, 748;
MS m/e 509 (MH^+);
Anal. Calcd for $C_{27}H_{24}N_8O_3 \cdot 0.55$ EtOAc: C, 62.97; H, 5.14; N, 20.12
Found: C, 63.22; H, 4.75; N, 19.73.

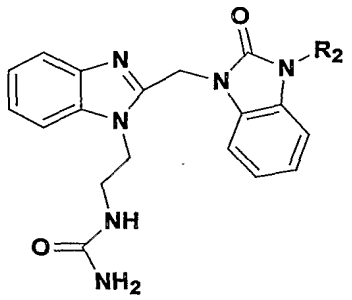
Compound 189



Compound **188** (100 mg, 0.19mmol) in methanol (10mL) was stirred with 1N NaOH (0.3 mL) at room temperature for 2 days, and then refluxed for 3 hours. The solvent was removed. The residue was diluted with water and acidified to pH 5 with 1N HCl. The white precipitate was filtered and dried under vacuum. The solid in methanol (5mL) was stirred with 0.5M NaOMe (0.34 mL) at room temperature under nitrogen for 3 hours. The solvent was evaporated and the residue was dried under vacuum to give 87mg (86% yield) of the sodium salt of compound **189** as a white solid:

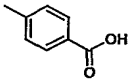
^{1}H NMR (DMSO-d_6) δ 4.92-5.0 (m, 4H), 5.09 (s, 2H), 5.27 (s, 2H), 6.99-7.29 (m, 9H), 7.53-7.56 (m, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.81 (s, 1H), 9.34 (s, 1H);
IR (KBr, cm^{-1}) 3412, 1698, 1566, 1492, 1390, 750;
MS m/e 495 (MH^+).

Compound 190

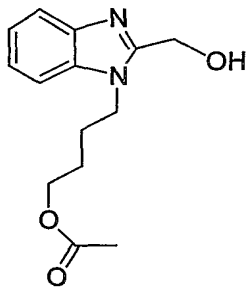


The tetrazole was dissolved in MeOH (30 ml) and NaOH (1N, 2 eq) was added and the mixture stirred for 12 h. The solvent removed and the resulting mixture was adjusted to pH 7 with 1N HCl. The product was extracted with EtOAc and the organic extracts were combined, dried over Na_2SO_4 and concentrated to give the products in the table below.

Table 16- Compound prepared as described for **190**.

#	R_2	^{1}H-NMR Data	MS Data
190a	$CH_2CH_2CH_2CO_2H$	1H NMR (DMSO-d6) d 1.86-1.90 (m, 2 H), 2.29 (t, *J* = 7.2, 2 H), 3.90 (t, *J* = 7.0, 2 H), 4.39 (t, *J* = 6.3, 2 H), 5.19 (s, 2 H), 5.36 (s, 2 H), 6.13 (t, *J* = 5.9, 1 H), 6.98-7.13 (m, 6 H), 7.19-7.24 (m, 2 H), 7.49-7.57 (m, 2 H), 12.06 (s, 1H);	MS m/e 437 (MH+);
190b		1H NMR (DMSO-d6) d 3.34 (t, J = 6.0, 2 H), 4.41 (t, *J* = 6.0, 2 H), 5.19 (s, 2 H), 5.42 (s, 2 H), 5.60 (s, 2 H), 6.16 (t, J = 5.9, 1 H), 6.99-7.02 (m, 2 H), 7.10-7.26 (m, 4 H), 7.45 (d, *J* = 8.2, 2), 7.50-7.58 (m, 2H), 7.90 (d, *J* = 8.2, 2H);	MS m/e 485 (MH+);
190c		1H NMR (DMSO-d6) d 3.35-3.40 (m, 2 H), 4.44 (t, J = 6.9 Hz, 2 H), 5.47 (s, 2 H), 5.56 (s, 2 H), 5.62 (s, 2 H), 6.85-7.02 (m, 4 H), 7.15-7.30 (m, 5 H), 7.52-7.61 (m, 2 H), 7.81-7.88 (m, 1 H);	MS m/e 521 (MH+);

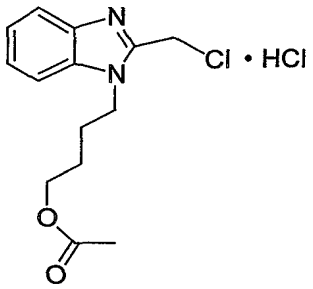
Compound 191



Compound **191** was prepared using the same procedure described for compound **4**, except that 3-methylbromobutane was replaced with 4-bromobutyl acetate.

^{1}H NMR ($CDCl_3$) δ 1.68-1.72 (m, 2H), 1.91-1.94 (m, 2H), 2.03 (s, 3H), 4.07 (t, J = 6.4 Hz, 2H), 4.26 (t, J = 7.5 Hz, 2H), 4.86 (s, 2H), 6.86 (bs, 1H), 7.20-7.29 (m, 3H), 7.65 (dd, J = 1.8, 6.7 Hz, 1H);
MS m/e 263 (MH^+).

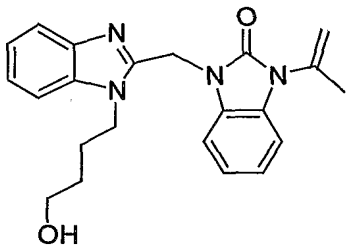
Compound 192



Compound **192** was prepared according to the same procedure described for compound **6**.

^{1}H NMR ($CDCl_3$) δ 1.80-1.86 (m, 2H), 2.03 (s, 3H), 2.06-2.12 (m, 2H), 4.14 (t, J = 6.1 Hz, 2H), 4.55 (t, J = 8.1 Hz, 2H), 5.42 (s, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H);
MS m/e 281 (MH^+).

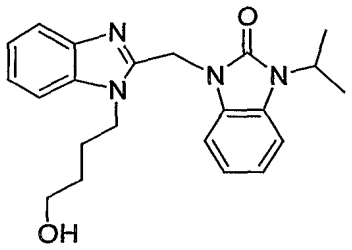
Compound 193



Compound **193** was prepared as described for compound **4**. The acetate group was removed by stirring with MeOH for 1 hour before work-up as previously described.

^{1}H NMR (DMSO-d6) δ 1.38-1.45 (m, 2H), 1.46-1.65 (m, 2H), 2.19 (s, 3H), 3.15-3.21 (m, 2H), 4.32-4.40 (t, J = 7.5 Hz, 2H), 4.40-4.46 (m, 1 H), 5.20 (s, 1H), 5.38 (s, 2H), 5.43 (s, 1H), 7.02-7.16 (m, 2H), 7.16-7.36 (m, 3H), 7.50-7.62 (m, 2H), 8.55 (s, 1H); MS m/e 376 (MH^+).

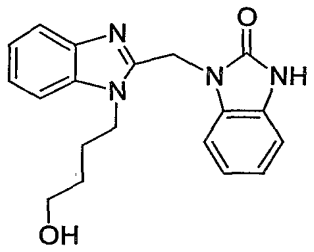
Compound 194



Compound **194** was prepared as described for compound **115**.

^{1}NMR (DMSO-d6) δ 1.39-1.45 (m, 2H), 1.46 (d, J = 6.9 Hz, 6H), 1.54-1.59 (m, 2H), 3.33-3.37 (m, 2H), 4.33 (t, J = 7.5 Hz, 2H), 4.45 (t, J = 5.1 Hz, 1H), 4.63-4.68 (m, 1H), 5.35 (s, 2H), 6.98-7.05 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 8.8 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H); MS m/e 378 (MH^+).

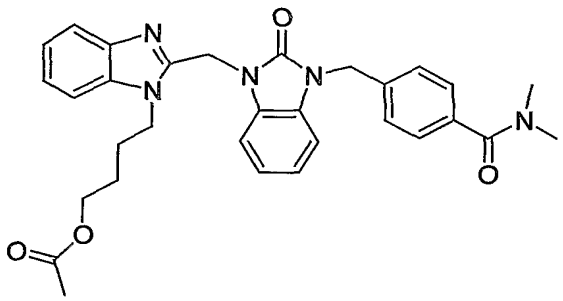
Compound 195



Compound **195** was prepared from compound **193** as described for compound **6**.

^{1}H NMR (DMSO-d6) δ 1.42-1.47 (m, 2H), 1.59-1.62 (m, 2 H), 3.36-3.40 (m, 2H), 4.33 (t, J = 7.5 Hz, 2H), 4.46 (t, J = 5.1 Hz, 2H), 5.32 (s, 2 H), 6.93-7.02 (m, 3H), 7.14-7.19 (m, 2H), 7.22-7.25 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H);
MS m/e 336 (MH^+).

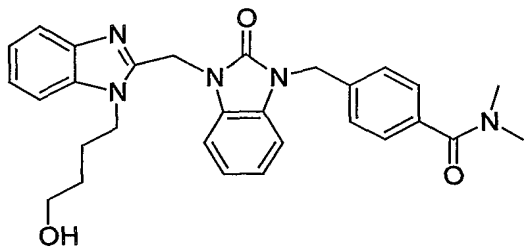
Compound 196



Compound **196** was prepared by alkylation of compound **195** with compound **90**.

^{1}H NMR (DMSO-d6) δ 1.60-1.68 (m, 2H), 1.69-1.79 (m, 2H), 1.96 (s, 3H), 2.86 (s, 3 H), 2.95 (s, 3H), 3.97 (t, J = 6.4 Hz, 2H), 4.37 (t, J = 7.15 Hz, 2H), 5.47 (s, 2H), 6.98-7.03 (m, 2H), 7.14-7.18 (m, 2H), 7.19-7.28 (m, 2H), 7.35-7.42 (m, 4H), 7.58 (dd, J = 2.9, 8.2 Hz, 2H);
MS m/e 539 (MH^+).

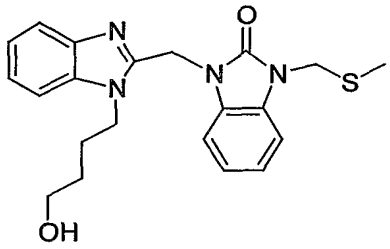
Compound 197



Compound **197** was prepared as described for compound **8.**

^{1}H NMR (DMSO-d6) δ 1.30-1.45 (m, 2H), 1.47-1.70 (m, 2H), 2.86-2.95 (m, 6H), 3.33-3.39 (m, 2H), 4.34-4.36 (m, 2H), 4.46-4.48 (m, 1H), 5.16 (s, 2 H), 5.43 (s, 2H), 6.95-7.11 (m, 2H), 7.14-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.36-7.47 (m, 3H), 7.49-7.59 (m, 3H);
MS m/e 496 (MH^+).

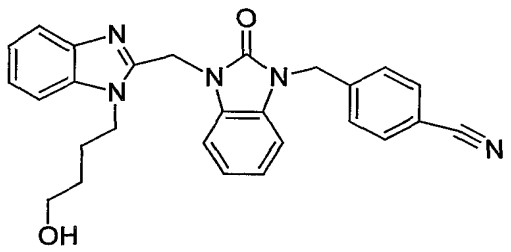
Compound 198



Compound **198** was prepared by alkylation of compound **195.**

^{1}H NMR (DMSO-d6) δ 1.59-1.62 (m, 2H), 1.76-1.79 (m, 2H), 1.99-2.02 (m, 2H), 2.54-2.63 (m, 4H), 3.93 (t, J = 4.1, 2H), 4.41 (t, J = 4.5, 2H), 5.41 (s, 2H), 6.99-7.19 (m, 4H), 7.24-7.28 (m, 2H), 7.56-7.60 (m, 2H);
MS m/e 413 (MH^+).

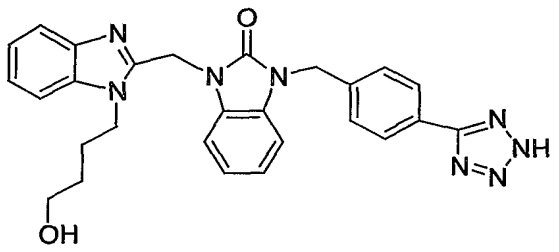
Compound 199



Compound **199** was prepared as described for compound **7** using Cs_2CO_3 as base.

^{1}H NMR (DMSO-d6) δ 1.41-1.48 (m, 2H), 1.64-1.71 (m, 2H), 3.36-3.38 (m, 2H), 4.35 (t, J = 7.8 Hz, 2H), 4.48 (t, J = 5.6 Hz, 1H), 5.23 (s, 2H), 5.43 (s, 2H), 7.01-7.04 (m, 2H), 7.14-7.28 (m, 4H), 7.52-7.60 (m, 4H), 7.84 (d, J = 8.2 Hz, 2H);
MS m/s 452 (MH^+).

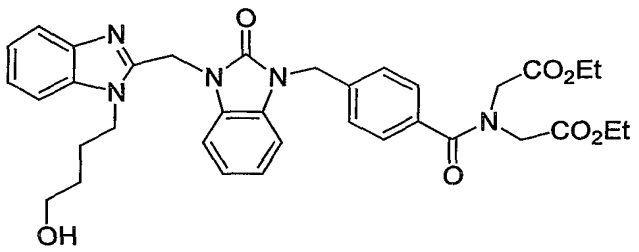
Compound 200



Compound **200** was prepared as described for compound **22**.

^{1}H NMR (DMSO-d6) δ 1.45-1.50 (m, 2H), 1.69-1.75 (m, 2H), 3.39 (t, J = 6.4 Hz, 2H), 4.44 (t, J = 7.4 Hz, 2H), 5.22 (s, 2H), 5.55 (s, 2H), 7.03-7.07 (m, 2H), 7.17-7.21 (m, 1 H), 7.27-7.30 (m, 2H), 7.34-7.37 (m, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H), 8.04 (d, J = 8.3 Hz, 2H);
MS m/e 495 (MH^+).

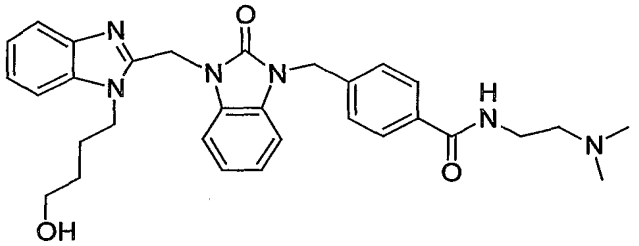
Compound 201



Compound **201** was prepared as described for compound **9** except EDC was used as coupling reagent.

^{1}H NMR (DMSO-d6) δ 1.11 (t, J = 6.9 Hz, 3H), 1.22 (t, J = 6.9 Hz, 3H), 1.20-1.38 (m, 2H), 1.65-1.80 (m, 2H), 3.41 (t, J = 6.3 Hz, 2H), 4.04-4.18 (m, 4H), 4.17 (s, 2 H), 4.40-4.52 (m, 2H), 5.17 (s, 2 H), 5.58 (s, 2H), 7.01-7.11 (m, 2H), 7.17-7.21 (m, 1H), 7.24-7.50 (m, 6H), 7.67 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 6.9 Hz, 1H);
MS m/e 598 (MH^+).

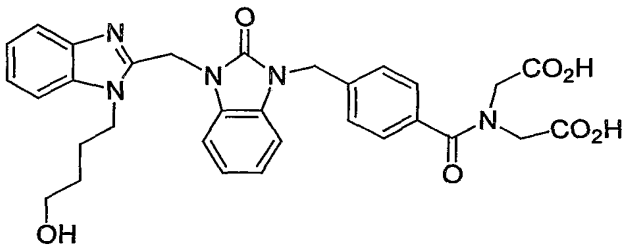
Compound 202



Compound **202** was prepared as described for compound **201**.

^{1}H NMR (DMSO-d6) δ 1.43-1.50 (m, 2H), 1.60-1.78 (m, 2H), 2.13 (s, 6H), 3.32-3.41 (m, 4H), 4.36 (t, J = 7.5 Hz, 2H), 4.61-4.68 (m, 2H), 5.17 (s, 2H), 5.43 (s, 2H), 6.99-7.05 (m, 2H), 7.09-7.26 (m, 3 H), 7.43 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7.2 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H), 8.35 (t, J = 5,7 Hz, 1H);
MS m/e 540 (MH^+).

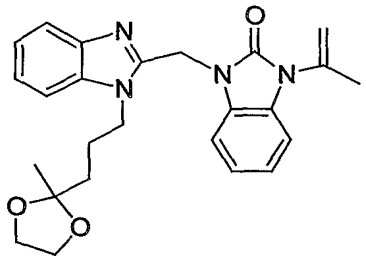
Compound 203



Compound **203** was prepared as described for compound **12**.

^{1}H NMR (DMSO-d6) δ 1.25-1.42 (m, 2H), 1.43-1.63 (m, 2H) 3.20-3.40 (m, 2H), 3.62 -3.82 (m, 2H), 4.21-4.39 (m, 2H), 4.72-4.92 (bs, 1H), 5.13 (s, 2H), 5.43 (s, 2H), 6.92-7.10 (m, 2H), 7.10-7.36 (m, 6H), 7.37-7.43 (m, 2H), 7.54-7.62 (m, 2H);
MS m/e 585 (MH^+).

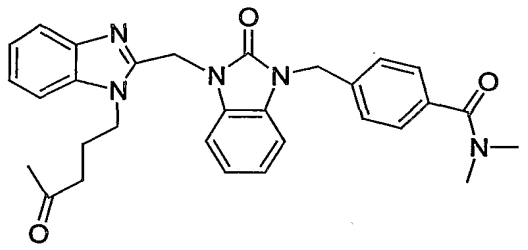
Compound 204



Compound **204** was prepared as described for compound **88** using 2-(3-chloro-propyl)-2-methyl-[1,3]dioxolane.

^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.55-1.72 (m, 4H), 2.25 (s, 3H), 3.67-3.71 (m, 2H), 3.81-3.84 (m, 2H), 4.33-4.36 (m, 2H), 5.27 (s, 1 H), 5.38 (s, 1 H), 5.42 (s, 2 H), 7.02-7.09 (m, 3H), 7.25-7.36 (m, 2H), 7.35-7.36 (m, 1H), 7.45-7.47 (m, 1H), 7.80-7.81 (m, 1H);
MS m/e 432 (MH^+).

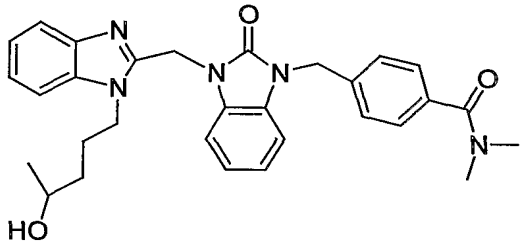
Compound 205



Compound **205** was prepared by deprotection of compound **204** as described for compound **6** followed by alkylation of the intermediate as described for compound **7**.

^{1}H NMR (DMSO-d6) δ 1.86-1.91 (m, 2H), 2.05 (s, 3H), 2.41-2.56 (m, 2H), 2.72-2.87 (m, 6H), 4.30-4.45 (m, 2H), 5.16 (s, 2H), 5.56 (s, 2H), 7.04-7.19 (m, 3H), 7.18-7.21 (m, 1H), 7.23-7.45 (m, 6H), 7.64 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H);
MS m/s 509 (MH^+).

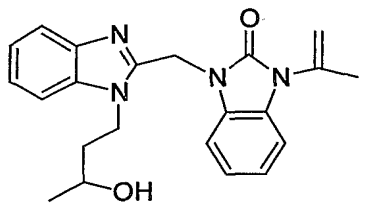
Compound 206



Compound **206** was prepared by $NaBH_4$ reduction of compound **205**.

^{1}H NMR (DMSO-d6) δ 0.96 (d, J = 6.1 Hz, 3H), 1.28-1.32 (m, 2H), 1.60-1.63 (m, 1H), 1.72-1.75 (m, 1H), 2.86 (s, 3H), 2.96 (s, 3H), 3.50-3.59 (m, 1H), 4.34 (t, J = 7.4 Hz, 2H), 4.41-4.48 (m, 1H), 5.16 (s, 2H), 5.43 (s, 2H), 7.0-7.02 (m, 2H), 7.15-7.18 (m, 2H), 7.22-7.26 (m, 2H), 7.36-7.42 (m, 4H), 7.55 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H);
MS m/e 511 (MH^+).

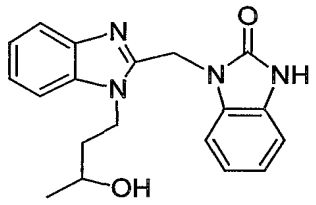
Compound 207



Compound **207** was prepared from compound **85** as described for compound **206**.

^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 6.18 Hz, 3 H), 1.67-1.78 (m, 1 H), 1.83-1.92 (m, 1 H), 2.25 (s, 3 H), 2.76 (d, J = 5.6 Hz, 1 H), 3.84-3.87 (m, 1 H), 4.43-4.52 (m, 2 H), 5.22 (s, 1 H), 5.40 (d, J = 1.4 Hz, 1 H), 5.46 (d, J = 4.5 Hz, 2 H), 7.08-7.12 (m, 3 H), 7.28-7.32 (m, 2 H), 7.37-7.40 (m, 1 H), 7.56-7.59 (m, 1 H), 7.79-7.82 (m, 1 H); MS m/e 377 (MH^+).

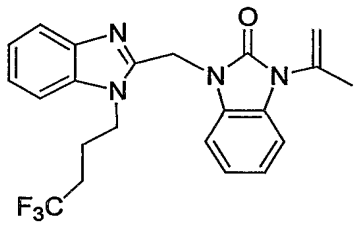
Compound 208



Compound **208** was prepared as described for compound **6**.

^{1}H NMR (DMSO-d6) δ 1.08 (d, J = 6.1 Hz, 3H), 1.77-1.82 (m, 2H), 3.62-3.74 (m, 1H), 4.56 (t, J = 7.1 Hz, 2H), 5.55-5.62 (m, 2H), 6.99-7.08 (m, 3H), 7.19 (d, J = 7.2 Hz, 1H), 7.43-7.53 (m, 2H), 7.69 (d, J = 7.4 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H); MS m/e 337 (MH^+).

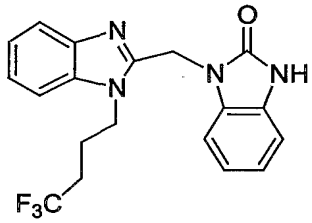
Compound 209



Compound **209** was prepared by alkylation of compound **3**.

^{1}H NMR ($CDCl_3$) δ 1.81-1.91 (m, 2H), 2.07-2.22 (m, 2H), 2.25 (s, 3H), 4.44 (t, J = 7.8 Hz, 2H), 5.21 (s, 1H), 5.40 (s, 3H), 7.06-7.10 (m, 3H), 7.27-7.33 (m, 3H), 7.52-7.62 (m, 1H), 7.80-7.84 (m, 1H);
MS m/e 415 (MH^+).

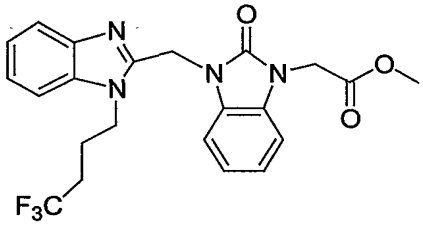
Compound 210



Compound **210** was prepared as described for compound **6**.

^{1}H NMR ($CDCl_3$) δ 1.76-1.86 (m, 2H), 2.10-2.27 (m, 2H), 4.41 (t, J = 8.0 Hz, 2H), 5.42 (s, 2H), 7.02-7.09 (m, 3H), 7.29-7.32 (m, 3H), 7.45-7.48 (m, 1H), 7.80-7.84 (m, 1H), 8.48 (s, 1H);
MS m/e 375 (MH^+).

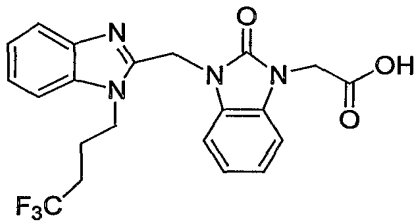
Compound 211



Compound **211** was prepared by alkylation of compound **210** as described for compound **7**.

^{1}H NMR ($CDCl_3$) δ 1.78-1.89 (m, 2H), 2.09-2.25 (m, 2H), 3.79 (s, 3H), 4.38 (t, J = 8.0 Hz, 2H), 4.67 (s, 2H), 6.87-6.92 (m, 1H), 7.05-7.12 (m, 1H), 7.29-7.32 (m, 3H), 7.47-7.50 (m, 1H), 7.81-7.84 (m, 1H);
MS m/e 447 (MH^+).

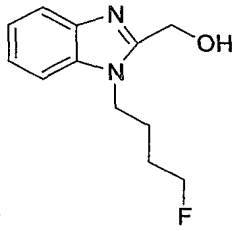
Compound 212



Compound **212** was prepared as described for compound **8**.

^{1}H NMR (DMSO-d6) δ 1.71-1.82 (m, 2H), 2.24-2.38 (m, 2 H), 4.05 (s, 2H), 4.39 (t, J = 7.7 Hz, 2H), 5.37 (s, 2H), 6.90-7.00 (m, 3H), 7.16-7.28 (m, 3H), 7.58 (d, J =7.8 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H);
MS m/e 433 (MH^+).

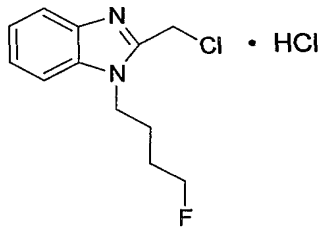
Compound 213



Compound **213** was prepared according to the same procedure described for compound **106** except that 3-methylbutylbromide was replaced with 1-bromo-4-fluorobutane.

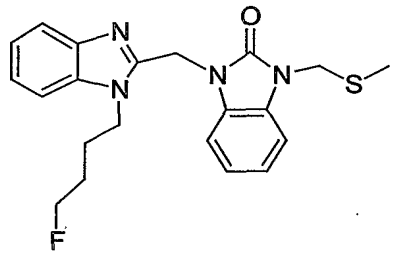
^{1}H NMR (DMSO-d_6) δ 1.65-1.75 (m, 2H), 1.85-1.90 (m, 2H), 4.32 (t, J = 7.5 Hz, 2H), 4.41 (t, J = 6.0 Hz, 1H), 4.51 (t, J = 6.0 Hz, 1H), 4.71 (d, J = 5.8 Hz, 2H), 5.62 (t, J = 5.8 Hz, 1H), 7.18 (t, J = 7.0 Hz, 1H), 7.23 (t, J = 6.3 Hz, 1H), 7.56-7.60 (m, 2H);
MS m/e 222 (MH^+).

Compound 214



Compound **214** was prepared according to the same procedure described for chloride **107** and was used immediately upon isolation.

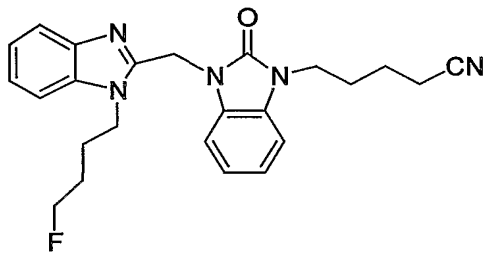
Compound 215



Compound **215** was prepared as described for compound **4**, followed by deprotection and alkylation as described for compound **7**.

^{1}H NMR (DMSO-d6) δ 1.71-1.84 (m, 4 H), 2.15 (s, 3 H), 4.12 (t, *J* = 3.5, 1 H), 4.50-4.54 (m, 3 H), 5.11 (s, 2 H), 5.65 (s, 2 H), 7.10-7.17 (m, 2 H), 7.34-7.38 (m, 2 H), 7.45-7.50 (m, 2 H), 7.71 (d, *J* = 4.8, 1H), 7.89 (d, *J* = 4.6, 1H);
MS m/e 399 (MH^+).

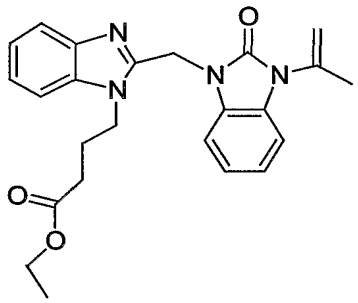
Compound 216



Compound **216** was prepared as described for compound **215** except 4-bromo-1-fluorobutane was used as the alkylating agent.

^{1}H NMR (DMSO-d6) δ 1.22-1.28 (m, 2H), 1.54-1.85 (m, 8H), 2.54-2.58 (m, 2H), 3.93 (t, J = 4.1, 2H), 4.35-4.40 (m, 2H), 5.39 (s, 2 H), 6.98-7.09 (m, 2H), 7.14-7.27 (m, 4H), 7.58 (t, J = 4.9, 2H);
MS m/e 420 (MH^+).

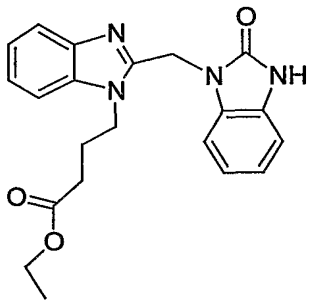
Compound 217



Compound **217** was prepared as described for compound **4**.

^{1}H NMR (DMSO-d6) δ 1.13 (t, J = 6.9 Hz, 3H), 1.80-1.95 (m, 2H), 2.17 (s, 3H), 2.37 (t, J = 7.2 Hz, 2H), 4.02 (q, J = 7.2 Hz, 2H), 4.36 (t, J = 6.6 Hz, 2 H), 5.19 (s, 1H), 5.39 (s, 1H), 5.42 (s, 1H), 7.06-7.10 (m, 2H), 7.11-7.28 (m, 4H), 7.58-7.71 (m, 2H);
MS m/e 418 (MH^+).

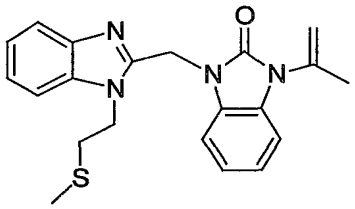
Compound 218



Compound **218** was prepared was described for compound **6**.

^{1}H NMR (DMSO-d6) δ 1.15 (t, J = 7.2 Hz, 3H), 1.81-1.98 (m, 2H), 4.02 (q, J = 7.2 Hz, 2H), 4.36 (t, J = 7.5 Hz, 2H), 5.32 (s, 2H), 6.91-7.08 (m, 3H), 7.15-7.30 (m, 3H), 7.58 (d, J = 8.1 Hz, 2H);
MS m/e 378 (MH^+).

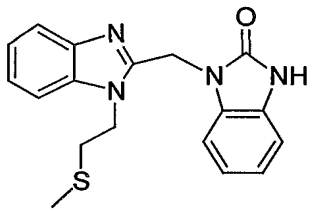
Compound 219



Compound **219** was prepared as described for compound **4** using 2-chloroethyl thiomethyl ether as the alkylating agent.

^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 2.25 (s, 3H), 2.75 (t, J = 6.9 Hz, 2 H), 4.62 (t, J = 6.9 Hz, 2H), 5.23 (d, J = 0.5 Hz, 1H), 5.40 (d, J = 1.4 Hz, 1H), 5.48 (s, 2H), 7.05-7.09 (m, 3H), 7.28-7.37 (m, 3H), 7.53-7.57 (m, 1 H), 7.79-7.84 (m, 1H);
MS m/e 379 (MH^+).

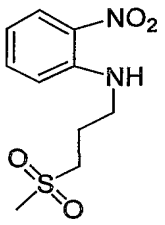
Compound 220



Compound **220** was prepared as described for compound **6**.

^{1}H NMR $CDCl_3$) δ 1.61 (s, 3H), 2.09 (s, 3H), 2.74 (t, J = 7.1 Hz, 2H), 4.59 (t, J = 7.1 Hz, 2H), 5.47 (s, 2H), 7.04-7.08 (m, 3H), 7.28-7.37 (m, 3H), 7.46-7.50 (m, 1H), 7.79-7.84 (m, 1H), 8.65 (bs, 1 H);
MS m/e 339 (MH^+).

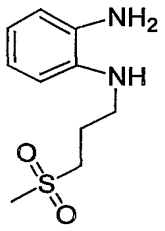
Compound 221



2-Fluoronitrobenzene (35.4 g, 250.9 mmol), 3-(methylthio)propylamine (24.0g, 228.1 mmol) and potassium carbonate (47.3 g, 342 mmol) were stirred in CH_3CN (100 mL) at room temperature overnight. After stirring for an additional hour at reflux, the mixture was cooled to room temperature and filtered. The filtrate was evaporated. To the residue in DMF (150 mL), magnesium monoperoxyphthalate hexahydrate (MMPP, 168 g, 340 mmol) was added in several portions with ice-water cooling. The mixture was stirred at room temperature for 3 hours and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH, water, brine, dried over $MgSO_4$ and evaporated. The residue was triturated with hot EtOAc to give compound **221** (48.7 g, 75% yield) as an orange solid.

^{1}H NMR ($CDCl_3$) δ 2.25-2.35 (m, 2H), 2.97 (s, 3H), 3.17 (t, J = 7.2 Hz, 2H), 3.59 (t, J = 6.9 Hz, 2H), 6.68 -6.74 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 7.45-7.51 (m, 1H), 8.20 (dd, J = 1.5, 8.7 Hz, 1H);
MS m/e 259 (MH^+);
Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.84
Found: C, 46.53; H, 5.54; N, 10.90.

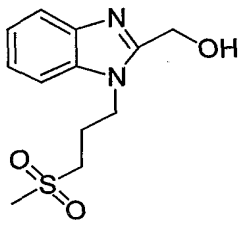
Compound 222



To a suspension of compound **221** (48.5 g, 187.8 mmol) in a mixture of $CHCl_3$ and MeOH (150 mL,1:3) was added 10% palladium on carbon (6 g) under nitrogen. The reduction was carried out in a Parr shaker with hydrogen pressure maintained between 40 and 60 psi for 25 minutes. The catalyst was removed by filtration through a pad of Celite and the filtrate was evaporated to give crude **222**.

^{1}H NMR (CD_3OD) δ 2.11-2.21 (m, 2H), 2.98 (s, 3H), 3.28-3.36 (m, 4H), 6.75 (dt, J = 0.9, 7.2 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 7.06-7.12 (m, 2H);
MS m/e 229 (MH^+).

Compound 223

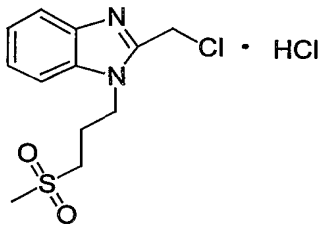


The crude diamine **222** obtained above was stirred at reflux overnight with glycolic acid (15.7 g, 207 mmol) in 6 N HCl (150 mL). The solution was cooled in an ice bath and neutralized with concentrated NH_4OH solution, extracted with

EtOAc, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (gradient, EtOAc/hexane, 1:1 to EtOAc/MeOH, 10:1) to give a product which crystallized from EtOAc/MeOH to afford 25.7 g (51% yield in two steps) of **223**.

^{1}H NMR (CD_3OD) δ 2.38-2.44 (m, 2H), 2.97 (s, 3H), 3.24 (t, J = 7.6 Hz, 2H), 4.54 (t, J = 7.6 Hz, 2H), 7.27 (t, J = 1.1, 8.1 Hz, 1H), 7.33 (dt, J = 1.1, 8.0 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 1.0, 8.0 Hz, 1H);
MS m/e 269 (MH^+).

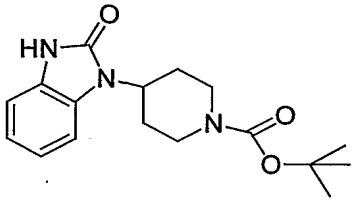
Compound 224



Compound **224** was prepared according to the same procedure described for compound **6**.

^{1}H NMR (CD_3OD) δ 2.46-2.52 (m, 2H), 3.03 (s, 3H), 3.37 (t, J = 7.1 Hz, 2H), 4.77 (t, J = 7.8 Hz, 2H), 5.31 (s, 2H), 7.68-7.73 (m, 2H), 7.86 (dd, J = 2.8, 6.9 Hz, 1H), 8.03 (dd, J = 1.7, 6.1 Hz, 1H);
MS m/e 287 (MH^+).

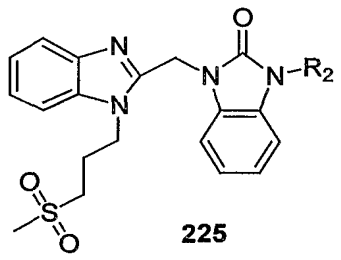
Compound 224a



To a solution of 4-(2-keto-1-benzimidazolinyl)piperidine (3.0 g, 13.8 mmol), triethylamine (2.79 g, 27.6 mmol) and DMAP (17 mg, 0.1 mmol) in CH_2Cl_2 (50 ml) was added di-*tert* butyldicarbonate (3.31 g, 15.2 mmol) at 0°C and stirred for 2 h.

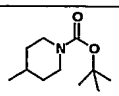
The reaction mixture was washed with $NaHCO_3$, dried and evaporated. The residue was purified by flash chromatography using hexanes:EtOAc (2:1 to 1:1) as eluant to give 2.68 g (61%) of compound **224a** as a white solid.

^1H NMR (CD_3OD) δ:1.49 (s, 9H), 1.75-2.02 (m, 2H), 2.29-2.43 (m, 2H), 2.89-2.99 (m, 2H), 4.23-4.29 (m, 2H), 4.37-4.46 (m, 1H), 7.02-7.07 (m, 3H), 7.19-7.22 (m, 1H);
MS m/e 318 (MH+).

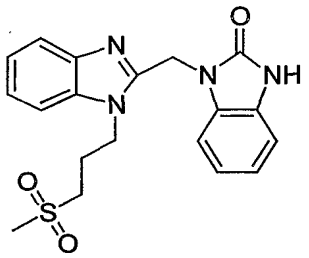


225

Table 17- Sulfones were prepared as described for compound **7** using chloride **224** and a benzimidazolone such as **224a** with Cs_2CO_3 as base. Compound **225d** was prepared from compound **225c** as described for compound **6**.

#	R_2	^{1}H-NMR Data	MS Data
225a	CH_3	($CDCl_3$) δ 1.61-1.67 (m, 2H), 1.85-1.91 (m, 2H), 2.13-2.19 (m, 2H), 2.83 (s, 3H), 3.05 (t, J = 7.2 Hz, 2H), 3.70 (t, J = 6.2 Hz, 2H), 3.99 (t, J = 7.0 Hz, 2H), 4.57 (t, J = 7.2 Hz, 2 H), 5.48 (s, 2H), 7.01-7.05 (m, 1H), 7.07-7.14 (m, 2H), 7.32-7.35 (m, 2H), 7.42-7.43 (m, 1H), 7.55-7.58 (m, 1H), 7.83-7.85 (m, 1H)	457 (MH+)
225b		(DMSO-d6) δ 2.07-2.15 (m, 2H), 2.18 (s, 3H), 2.98 (s, 3H), 3.21 (t, J = 7.4 Hz, 2H), 4.50 (t, J = 7.4 Hz, 2 H), 5.22 (s, 1H), 5.40-5.41 (m, 3H), 7.06-7.09 (m, 2H), 7.16-7.32 (m, 4H), 7.38-7.64 (m, 2H)	425 (MH+)
225c		($CDCl_3$) δ 1.52 (s, 9H), 1.82-1.88 (m, 2H), 2.18-2.38 (m, 4H), 2.85 (s, 3H), 2.86-2.94 (m, 2H), 3.04 (t, J = 7.3 Hz, 2H), 4.27-4.38 (m, 2H), 4.40-4.49 (m, 1H), 4.62 (t, J = 7.5 Hz, 2H), 5.49 (s, 2H), 7.07-7.15 (m, 2H), 7.36-7.39 (m, 2H), 7.44-7.49 (m, 1H), 7.63-7.66 (m, 1H), 7.84-7.88 (m, 1H)	568 (MH+)
225d		(CD_3OD) δ 2.12-2.16 (m, 2H), 2.44-2.48 (m, 2H), 2.76-2.80 (m, 2H), 3.02 (s, 3H), 3.22-3.28 (m, 2H), 3.32-3.35 (m, 2H), 3.58-3.65 (m, 2H), 4.64-4.69 (m, 1H), 4.83 (t, J = 7.9 Hz, 2H), 5.79 (s, 2H), 7.20-7.28 (m, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.65-7.72 (m, 2H), 7.75 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H)	468 (MH+)

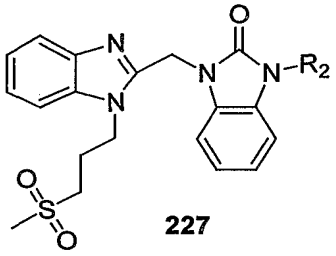
Compound 226



Compound **226** was prepared as described for compound **6**.

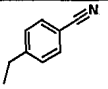
^{1}H NMR (DMSO-d6) δ 2.03-2.14 (m, 2H), 2.97 (s, 3H), 3.21 (t, J = 8.0 Hz, 2H), 4.48 (t, J = 7.4 Hz, 2H), 5.34 (s, 2H), 6.95-7.02 (m, 3H), 7.16-7.29 (m, 3H), 7.57-7.63 (m, 2H);

MS m/e 385 (MH^+).



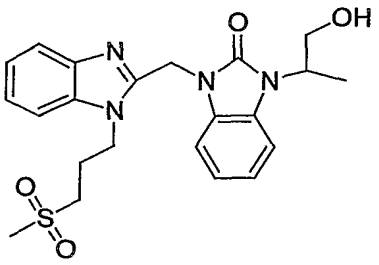
227

Table 18- Compounds were prepared by alkylation of **226** as described for compound **7**.

#	R_2	^{1}H-NMR Data	MS Data
227a		($CDCl_3$) δ 2.16-2.26 (m, 2 H), 2.90 (s, 3 H), 3.08 (t, J = 7.3 Hz, 2 H), 4.58 (t, J = 7.7 Hz, 2 H), 5.45 (s, 2 H), 7.18-7.23 (m, 2 H),7.35-7.45 (m, 4 H), 7.62-7.66 (m, 1 H), 7.81-7.86 (m, 1 H)	435 (MH+)
227b[a]		($CDCl_3$) δ 1.61-1.67 (m, 2 H), 1.85-1.91 (m, 2 H), 2.13-2.19 (m, 2 H), 2.83 (s, 3 H), 3.05 (t, J = 7.2 Hz, 2 H), 3.70 (t, J = 6.2 Hz, 2 H), 3.99 (t, J = 7.0 Hz, 2 H), 4.57 (t, J = 7.2 Hz, 2 H), 5.48 (s, 2 H), 7.01-7.05 (m, 1 H), 7.07-7.14 (m, 2 H), 7.32-7.35 (m, 2 H), 7.42-7.43 (m, 1 H), 7.55-7.58 (m, 1 H), 7.83-7.85 (m, 1 H)	457 (MH+)
227c[a]		(DMSO-d6) δ 2.12-2.17 (m, 2 H), 3.00 (s, 3 H), 3.22 (t, J = 7.9 Hz, 2 H), 4.50 (t, J = 8.0 Hz, 2 H), 5.23 (s, 2 H), 5.47 (s, 2 H), 7.01-7.06 (m, 2 H), 7.13-7.22 (m, 2 H), 7.28-7.31 (m, 2 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.58-7.65 (m, 2 H), 7.83 (d, J = 8.2 Hz, 2 H)	500 (MH+)

a, Cs_2CO_3 was used as base instead of BTPP.

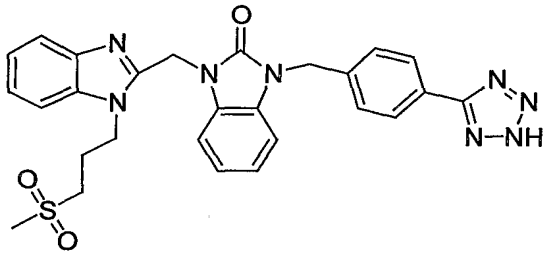
Compound 228



To a solution of **225b** (42 mg, 0.1 mmol) in THF (1 ml) was added 9-BBN (0.5 M in THF) (1.0 ml, 0.5 mmol) at 0°C and the final solution was stirred for 12 h. The reaction mixture was quenched with 1 M NaOH (2 ml) and 30% H_2O_2 (1 ml) and the mixture was stirred for 2 h then extracted with EtOAc. The organic layer was washed with brine, dried, evaporated. The residue was purified by preparative reverse phase HPLC to yield 28 mg (63%) of **228** as a hygroscopic solid.

^{1}H NMR (CD_3OD) δ 1.54 (d, J = 7.1 Hz, 3H), 2.41-2.47 (m, 2H), 3.00 (s, 3H), 3.31-3.32 (m, 2H), 3.82-3.86 (m, 1H), 4.14-4.18 (m, 1H), 4.61-4.66 (m, 1H), 4.76 (t, J = 7.6 Hz, 2H), 5.70 (s, 2H), 7.13-7.21 (m, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.53-7.62 (m, 2 H), 7.69 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H);
MS m/e 443 (MH^+).

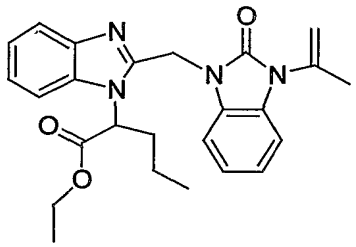
Compound 229



Compound **229** was prepared as described for compound **52**.

^{1}H NMR (DMSO-d6) δ 2.12-2.17 (m, 2H), 3.00 (s, 3H), 3.24 (t, J = 7.7 Hz, 2H), 4.52 (t, J = 7.4 Hz, 2H), 5.22 (s, 2H), 5.48 (s, 2H), 7.031-7.06 (m, 2H), 7.16-7.22 (m, 2H), 7.26-7.31 (m, 2H), 7.57-7.60 (m, 3H), 7.64 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.3 Hz, 2H);
MS m/e 543 (MH^+).

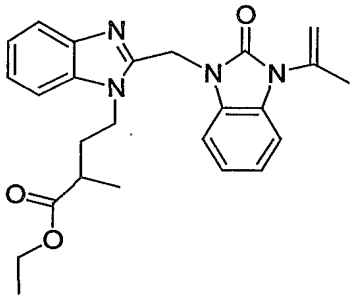
Compound 230



Compound **230** was prepared as described compound **4**.

^{1}H NMR ($CDCl_3$) δ 0.77 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.1 Hz, 3H), 0.90-0.98 (m, 1H), 1.20-1.29 (m, 1H), 2.13-2.35 (m, 2H), 2.24 (s, 3H), 3.78-3.94 (m, 2H), 5.19 (s, 1H), 5.36 (d, J = 15.8 Hz, 1H), 5.39 (d, J = 1.4 Hz, 1H), 5.51 (d, J = 15.7 Hz, 1H), 5.52-5.57 (m, 1H), 7.01-7.09 (m, 3H), 7.21-7.31 (m, 2H), 7.37 (d, J = 7.3 Hz, 1H), 7.44-7.46 (m, 1H), 7.82 (d, J = 7.4 Hz, 1H);
MS m/e 433 (MH^+).

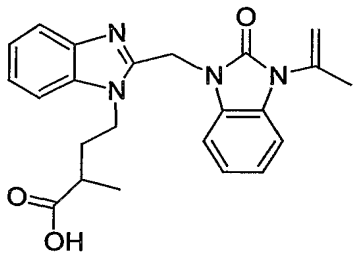
Compound 231



Compound **231** was prepared as described for compound **4**.

^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 7.1 Hz, 3H), 1.52-1.64 (m, 1H), 2.03-2.15 (m, 1H), 2.25 (s, 3 H), 2.53-2.62 (m, 1H), 3.67 (s, 3H), 4.29-4.50 (m, 2H), 5.21 (s, 1H), 5.39 (d, J = 1.1 Hz, 1H), 5.34-5.48 (m 2H), 7.04-7.12 (m, 3H), 7.25-7.34 (m, 2H), 7.40-7.44 (m, 1H), 7.49-7.53 (m, 1H), 7.77-7.83 (m, 1H);
MS m/e 405 (MH^+).

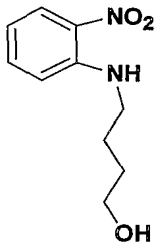
Compound 232



Compound **232** was prepared as described for compound **8**.

^{1}H NMR(CD_3OD) δ 1.15 (d, J = 7.1 Hz, 3 H), 1.50-1.64 (m, 1 H), 1.99-2.11 (m, 1 H), 2.27 (s, 3 H), 2.29-2.43 (m, 1 H), 4.35-4.44 (m, 2 H), 5.29 (s, 1 H), 5.40-5.59 (m, 3 H), 7.04-7.34 (m, 5 H), 7.59 (d, J = 8.2 Hz, 1 H), 7.66 (d, J = 7.5 Hz, 1 H);
MS m/e 405 (MH^+).

Compound 233 (Scheme III)

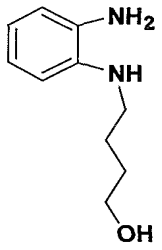


A solution of 2-fluoronitrobenzene (5.0 g, 35.5 mmol) and 1-amino-4-butanol (3.2 g, 35.5 mmol) in CH_3CN (100 mL) and triethylamine (3.80 g, 35.5 mmol) was heated to reflux for 12 h, and evaporated. The residue was dissolved in ethyl acetate and washed with 1N HCl, dried over magnesium sulfate and evaporated to give 7.21 g (97% yield) of compound **233** as a dark orange solid:

^{1}H NMR (DMSO-d_6) δ 1.45-1.56 (m, 2H), 1.58-1.69 (m, 2H), 3.35 (t, J = 6.7 Hz, 2H), 3.43 (t, J = 6.4 Hz, 2H), 3.90-4.0 (br, 1H, exchanges with D_2O), 6.66 (t, J = 6.0 Hz, 1H); 7.04 (d, J = 9.0 Hz, 1H);.7.52 (t, J = 7, 2 Hz, 1H); 8.04 (d, J = 7.2 Hz, 1H); 8.13 (br s, 1H, exchanges with D_2O);
IR (KBr cm^{-1}) 1350, 1154;
MS m/e 211 (MH^+);
Anal. Calcd for $C_{10}H_{14}N_2O_3 \cdot 0.28\ H_2O$: C, 55.80; H, 6.82; N, 13.01

Found: C, 55.80; H, 6.62; N, 12.97.

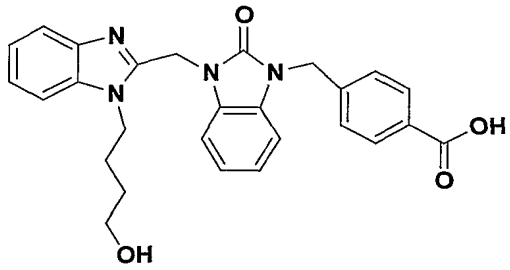
Compound 234



A mixture of nitro compound **233** (5.0 g, 23.8 mmol) and 10% Pd/C (100 mg) in ethanol (50 mL) was hydrogenated at 40 psi for 4 h. The catalyst was removed by filtration and the filtrate was evaporated to give 4.3 g (99% yield) of compound **234** as a dark oil:

^{1}H NMR(DMSO-d_6) δ 1.47-1.66 (m, 4 H), 2.99 (t, J = 6.6 Hz, 2 H), 3.43 (t, J = 6.6 Hz, 2 H), 4.31-4.5(br, 4 H, exchange with D_2O), 6.36-6.42 (m, 2 H) 6.54-6.82 (m, 2 H);
IR (film, cm^{-1}) 1055, 739;
MS m/e 181 (MH^+);
Anal. Calcd for $C_{10}H_{16}N_2O \cdot 0.71\ H_2O$: C, 62.23; H, 9.10; N, 14.51
Found: C, 62.23; H, 8.78; N, 14.41.

Compound 235

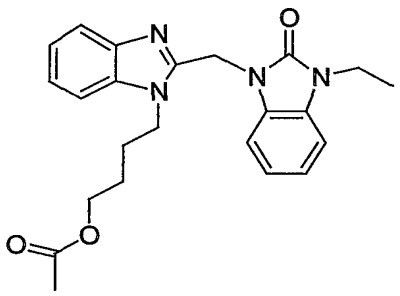


To a solution of diamine **234** (1.0 g, 6.0 mmol) in methylene chloride (50 mL) at -78 °C was added a solution of an acid chloride which was prepared from the acid **125** (2.05 g, 6.02 mmol) with excess $SOCl_2$, followed by addition of triethylamine (0.97 mL, 7.0 mmol). The mixture was stirred at -78°C for 1 hr then at room temperature for 12 h. The solvent was evaporated and the black residue (2.7 g)

was dissolved in acetic acid and heated to reflux for 4h. The solvent was evaporated. The black residue was purified by chromatography on silica gel and eluted with 3% methanol in methylene chloride to give 2.3 g of a mixture of esters as a yellow oil. The mixture in methanol (20 mL) was treated with 1N sodium hydroxide (10 mL, 10 mmol) and heated to reflux for 1 h, and concentrated under reduced pressure. The precipitate was filtered to give 0.65 g (31% yield) of the sodium salt of compound **235** as a white solid: mp >240°C;

^{1}H NMR (DMSO-d6) δ 1.47-1.40 (m, 2 H), 1.68-1.60 (m, 2 H), 3.37 (t, J = 6.3Hz, 2 H), 4.35 (t, J = 7.5Hz, 2 H), 5.15 (s, 2 H), 5.43 (s, 2 H), 7.03-6.99 (m, 2 H), 7.38-7.15 (m, 3 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.57 (d, J = 7.2 Hz, 1 H), 7.87 (d, J = 8.1 Hz, 2 H);
IR (KBr cm^{-1}) 1701, 750;
MS m/e 471 (MH^+);
HRMS m/e (M^+) calcd for $C_{27}H_{26}N_4O_4$: 470.1954, found 470.2039.

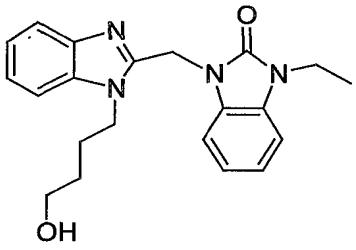
Compound 236



Compound **236** was prepared as described for compound **235** using compound **169**.

^{1}H NMR (DMSO-d6) δ 1.23 (t, J = 7.1 Hz, 3H), 1.45-1.55 (m, 4H), 19.2 (s, 3H), 3.50-3.61 (m, 2H), 3.81-3.90 (m, 4H), 4.25-4.35 (m, 1H), 5.35 (s, 2H), 6.97-7.15 (m, 2H), 7.15-7.25 (m, 4H), 7.53-7.60 (m, 2H);
MS m/e 406 (MH^+)

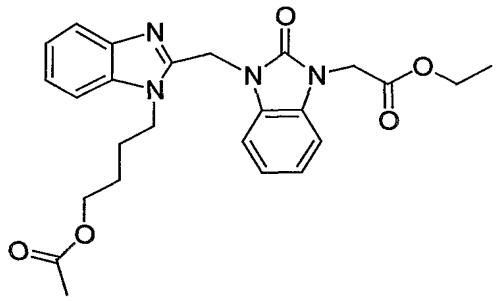
Compound 237



Compound **237** was prepared from compound **236** as described for compound **8**.

^{1}H NMR (DMSO-d6) δ 1.23 (t, J = 7.1 Hz, 3H), 1.30-1.45 (m, 2H), 3.20-3.40 (m, 2H), 1.45-1.60 (m, 2H), 3.20-3.40 (m, 2H), 3.92 (q, J = 7.2 Hz, 2H), 4.33 (t, J = 7.3 Hz, 2 H), 4.46(t, J = 5.0 Hz, 1H), 5.36 (s, 2H), 6.97-7.12 (m, 2H), 7.12-7.25 (m, 4H), 7.52-7.59 (m, 2H);
MS m/e 364 (MH^+).

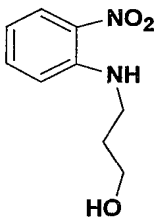
Compound 238



Compound **238** was prepared as described for compound **235** before the hydrolysis step.

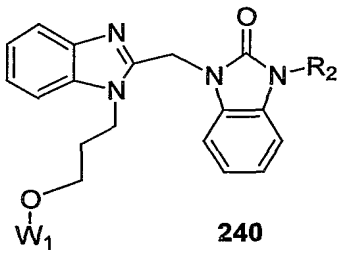
^{1}H NMR (DMSO-d6) δ 1.22 (t, J = 6.2 Hz, 3H), 1.53-1.78 (m, 4H), 1.97 (s, 3H), 3.99 (t, J = 6.0 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.35 (t, J = 6.6 Hz, 2H), 4.79 (s, 2H), 5.40 (s, 2H), 7.04-7.07 (m, 2H), 7.08-7.31 (m, 4H), 7.56 (t, J = 8.1 Hz, 2H);
MS m/e 464 (MH^+).

Compound 239



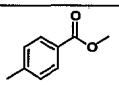
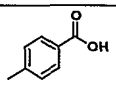
Compound **239** was prepared from 1-aminopropanol and 2-fluoronitrobenzene as previously described for compound **233**.

^{1}H NMR ($CDCl_3$) δ 1.97-2.02 (m, 2H), 3.46-3.50 (m, 2H), 3.84-3.87 (m, 2H), 6.64 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 7.43 (t, J = 7.05 , 1H), 8.17 (d, J = 7.2 Hz, 1H);
MS m/e 166 (MH^+).



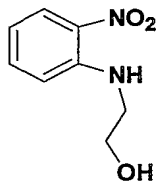
240

Table 20- Compounds were prepared as described for compound **235**. The acetates were removed by mild acid hydroylsis.

#	W_1	R_2	^{1}H-NMR Data	MS Data
240a	OAc[a]	Et	(DMSO-d6) 1.23 (t, J = 7.3 Hz, 3 H), 1.90-2.10 (m, 2 H), 1.97 (s, 3 H), 3.92 (q, J = 7.2 Hz, 2 H), 3.99-4.06 (m, 2 H), 4.42 (t, J = 7.3 Hz, 2 H), 5.37 (s, 2 H), 6.98-7.08 (m, 2 H), 7.14-7.25 (m, 4 H), 7.53-7.60 (m, 2H)	392 (MH+)
240b	H[b]	Et	DMSO-d6: 1.24 (t, J = 7.0 Hz, 3H), 1.76-1.82 (m, 2H), 3.39-3.42 (m, 2H), 3.92 (q, J = 7.0 Hz, 2H), 4.40 (t, J = 7.1 Hz, 2H), 4.71 (t, J = 4.8 Hz, 1H), 5.39 (s, 2H), 7.01-7.14 (m, 2H), 7.15-7.26 (m, 4H), 7.55 (t, J = 8.6 Hz, 2H)	350 (MH+)
240c	OAc	CH_2CO_2Et	DMSO-d6: 1.21 (t, J = 7.1 Hz, 3H), 1.89-2.02 (m, 2H), 1.98 (s, 3H), 4.10 (t, J = 6.1 Hz, 2H), 4.16 (q, J =7.1 Hz, 2H), 4.15 (t, J = 7.4 Hz, 2H), 4.79 (q, J = 7.1 Hz, 2H), 5.40 (s, 2H), 7.01-7.08 (m, 2H), 7.15-7.28 (m, 4H), 7.55 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H)	450 (MH+)
240d	H	CH_2CO_2H	(DMSO-d6) 1.59-1.65 (m, 2 H), 3.35 (t, J = 6.2 Hz, 2 H), 4.12 (s, 2 H), 4.33 (t, 7.2 Hz, 2 H), 5.35-5.38 (m, 2 H), 6.89-7.01 (m, 3 H), 7.11-7.25 (m, 3 H), 7.52 (d, J = 7.4 Hz, 1 H), 7.58 (d, J = 7.3 Hz, 1 H)	380 (MH+)
240e[c]	H		(DMSO-d6) 1.80-1.94 (m, 2 H), 3.42 (t, J = 7.2 Hz, 2 H), 3.82 (s, 3 H), 4.51 (t, J = 6.8 Hz, 2 H), 5.20 (s, 2 H), 5.60 (s, 2 H), 7.01-7.07 (m, 2 H), 7.12-7.16 (m, 1 H), 7.23-7.26 (m, 1 H), 7.25-7.40 (m, 2 H), 7.48 (d, J = 7.3 Hz, 2 H), 7.63 (d, J = 7.3 Hz, 1 H), 7.73 (d, J = 7.9 Hz, 1 H), 7.93 (d, J = 7.3 Hz, 2 H)	470 (MH+)
240f	H		(DMSO-d6) 1.84 (m, 2 H), 3.31-3.45 (m, 2 H), 4.35-4.45 (m, 2 H), 4.78-4.91 (m, 1 H), 5.10(s, 2 H), 5.46 (s, 2 H), 6.92-7.09 (m, 2 H), 7.10-7.38 (m, 6 H), 7.56 (d, J = 7.8 Hz, 2 H), 7.81 (d, J = 7.5 Hz, 2 H)	456 (MH+)

a, acetate is isolated by silica gel chromatography prior to hydrolysis; **b,** hydrolysis carried out as described for compound 4; **c,** cyclization step carried using TFA instead of AcOH.

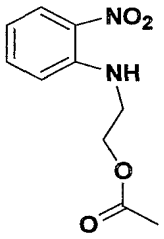
Compound 241



Compound **241** was prepared by addition of ethanolamine to 2-fluoronitrobenzene as previously described for compound **233**.

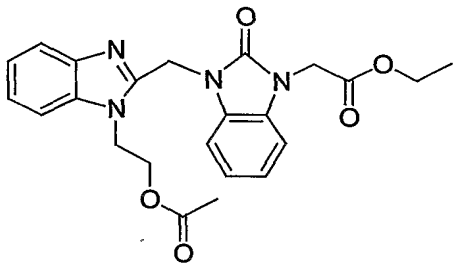
^{1}H NMR ($CDCl_3$) δ 3.39-3.43 (m, 2H), 3.63-3.69 (m, 2H), 6.68 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 7.53 (t, J = 6.9 Hz, 1H), 8.06 (d, 8.7 Hz, 1H), 8.23-8.35 (m, 1H);
MS m/e 196 (MH^+).

Compound 242



To a solution of 2-(2-nitro-phenylamino)-ethanol (2 g, 10.97 mmol) in CH_2Cl_2 (70 ml) were added triethylamine (2.77 g, 27.37 mmol) and acetic anhydride (1.68 g, 16.45 mmol). The mixture was refluxed overnight. The next day it was diluted with CH_2Cl_2 and washed with 1N HCl, and brine. The organic layer was dried over Na_2SO_4 and concentrated to give 2.40 g (98% yield) of compound **242** as yellow solid.

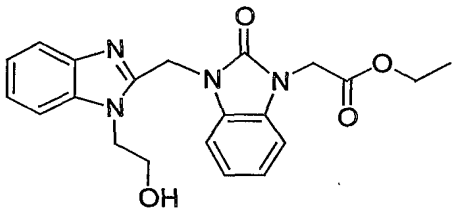
Compound 243



Compound **243** was prepared as described for compound **170** using acetic acid 2-(2-amino-phenylamino)-ethyl ester and (3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid as described for compound **170**.

^{1}H NMR (DMSO-d6) δ 1.22 (t, *J* = 7.1, 3H), 1.90 (s, 3H), 4.16 (q, J = 7.1, 2H), 4.35 (t, J = 5.0, 2H), 4.68 (t, J = 5.1, H), 4.79 (s, 2H), 5.45 (s, 2H), 7.03-7.10 (m, 2H), 7.15-7.27 (m, 4H), 7.55-7.62 (m, 2H);
MS m/e 437 (MH^+).

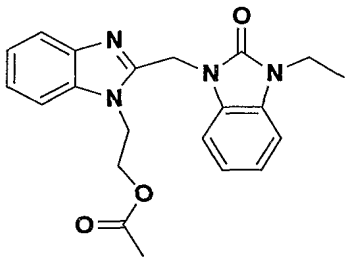
Compound 244



To a solution of compound **243** (570 mg, 1.30 mmol) in EtOH (40 ml) was added 3 drops of H_2SO_4 and the solution was refluxed overnight. The solvent was evaporated. The residue was diluted with EtOAc and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, and evaporated to give 473 mg (92% yield) of compound **244** as a white solid.

^{1}H NMR (DMSO-d6) δ 1.22 (t, *J* = 7.1, 3 H), 3.71 (t, J = 4.8, 2 H), 4.17 (q, J = 7.1, 2 H), 4.46 (t, *J* = 4.9, 2 H), 4.78 (s, 2 H), 5.11 (s, 1 H), 5.45 (s, 2 H), 7.00-7.08 (m, 2 H), 7.12-7.24 (m, 4 H), 7.53-7.57 (m, 2 H);
MS m/e 395 (MH^+)

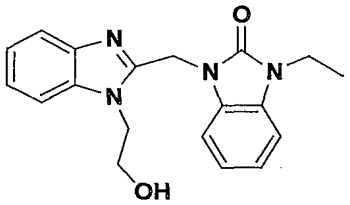
Compound 245



Compound **245** was prepared as described for compound **236**.

^{1}H NMR (DMSO-d6) δ 1.24 (t, J = 7.2 Hz, 3H), 1.87 (s, 3H), 3.93 (t, J = 7.6 Hz, 2H), 4.32 (t, J = 4.8 Hz, 2 H), 4.69 (t, J = 5.1 Hz, 2H), 5.42 (s, 2H), 7.03-7.18 (m, 2H), 7.19-7.31 (m, 2 H), 7.55-7.61 (m, 2H);
MS m/e 378 (MH^+).

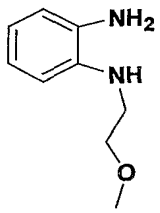
Compound 246



Compound **246** was prepared as described for compound **240b**.

^{1}H NMR (DMSO-d6) δ 1.25 (t, J = 6.6 Hz, 3H), 3.60-3.70 (m, 2H), 3.93 (q, J = 7.2 Hz, 2H), 4.47 (t, J = 5.1 Hz, 2H), 5.09 (t, J = 5.1 Hz, 1H), 5.42 (s, 2H), 7.00-7.11 (m, 2H), 7.11-7.27 (m, 4H), 7.52-7.57 (m, 2H);
MS m/e 336 (MH^+).

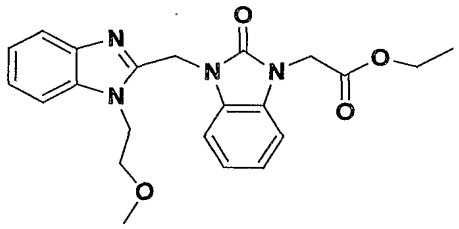
Compound 247



Compound **247** was prepared as previously described for compound **234** using 2-methoxyethylamine.

^{1}H NMR ($CDCl_3$) δ 3.18 (dt, 5.7, 6.0 Hz, 2H), 3.21 (s, 3H), 3.53 (t, J = 5.7 Hz, 2H), 4.32-4.40 (m, 1H), 4.40-4.49 (s, 2H), 6.42-6.56 (m, 4H);
MS m/e 166 (MH^+).

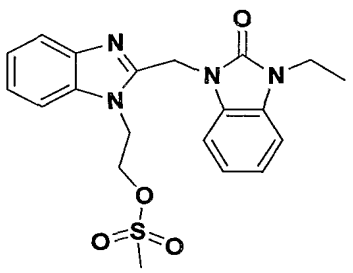
Compound 248



Compound **248** was prepared as described for compound **235** using N-(2-methoxy-ethyl)-benzene-1,2-diamine and (3-ethoxycarbonylmethyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid.

^{1}H NMR (DMSO-d6) δ 1.23 (t, J = 6.9 Hz, 3H), 3.19 (s, 3H), 3.28-3.72 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.51-4.62 (m, 2H), 4.79 (s, 2H), 5.42 (s, 2H), 7.01-7.06 (m, 2H), 7.19-7.25 (m, 4H), 7.56 (d, J = 8.1 Hz, 2H);
MS m/e 408 (MH^+).

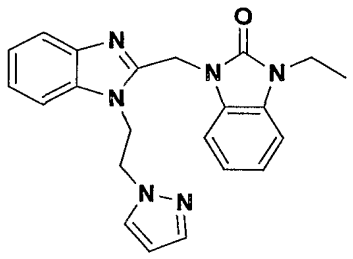
Compound 249



To a 0°C solution of compound **246** (2.38 g, 0.71 mmol) in CH_2Cl_2 (100 ml) was added Et_3N (0.12 ml, 0.9 mmol) followed by methanesulfonyl chloride (0.085 ml, 0.75 mmol). The mixture was warmed to room temperature, stirred for 12 h then poured into 1N HCl. The organic layer was separated and dried over $MgSO_4$ and concentrated to give 0.196 mg (67%) of compound **249** as a white solid.

^{1}NMR (DMSO-d6) δ 1.25 (t, J = 7.2 Hz, 3H), 3.01 (s, 3H), 3.82-3.99 (m, 2H), 4.54 (t, J = 5.4 Hz, 2H), 4.76 (m, J = 5.4 Hz, 2H), 5.41 (s, 2H), 7.02-7.12 (m, 3H), 7.15-7.34 (m, 3H), 7.51-7.65 (m, 2H);
MS (m/e) 414 (MH^+)

Compound 250

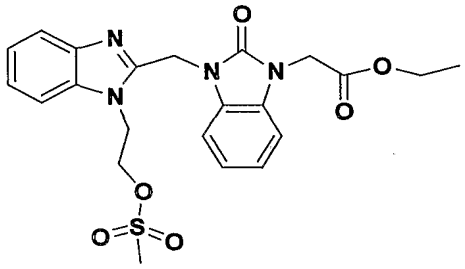


To a slurry of NaH (38 mg, 0.95 mml) in DMF (5 ml) was added pyrazine (63 mg, 0.92 mmol) followed by a solution of mesylate prepared above. The mixture was stirred at 23°C for 12 h. The solvent was removed and the residue dissolved in EtOAc and washed with water. The organic layers was dried over $MgSO_4$ concentrated and the residue chromatographed (3 % MeOH/CH_2Cl_2 as eluant to give compound **250** as a clear glass (120 mg, 85% yield).

^{1}H NMR (DMSO-d6) δ 1.23 (t, J = 6.9Hz, 3H), 3.92 (q, J = 7.2Hz, 2H), 4.55 (t, J = 5.3Hz, 2H), 4.80 (t, J = 4.8Hz, 2H), 4.94 (s, 2H), 6.17-6.19 (m, 1H), 7.00-7.25 (m, 6H), 7.27-7.58 (m, 3H);

MS (m/e) 386 (MH^+).

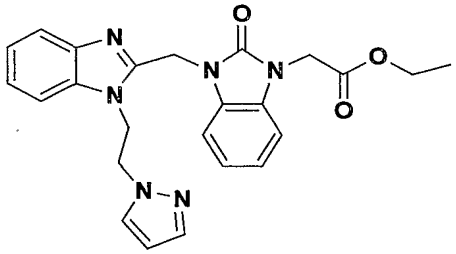
Compound 251



Compound **251** was prepared from compound **244** as described for compound **249** above.

^{1}H NMR (DMSO-d6) δ 1.18-1.23 (m, 3H), 3.06 (s, 3H), 4.11-4.20 (m, 3H), 4.56-4.59 (m, 2H), 4.59-4.84 (m, 3H), 5.52 (s, 2H), 7.05-7.11 (m, 2H), 7.16-7.35 (m, 4H), 7.62 (d, J = 7.4Hz, 1H), 7.72 (d, J = 8.0, 1H);
MS (m/e) 473 (MH^+)

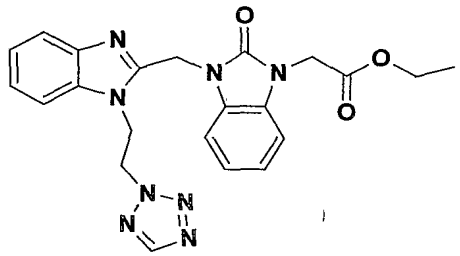
Compound 252



Compound **252** was prepared from compound **251** as described for compound **250** above.

^{1}H NMR (DMSO-d6) δ 1.19 (t, J = 7.1, 3H), 4.14 (q, J = 7.1, 2H), 4.50-4.54 (m, 2H), 4.75-4.79 (m, 3H), 5.00 (s, 2H), 6.17 (s, 1H), 7.00-7.07 (m, 2H), 7.10-7.20 (m, 3H), 7.34-7.41 (m, 2H), 7.46-7.53 (m, 2H);
MS (m/e) 445 (MH^+).

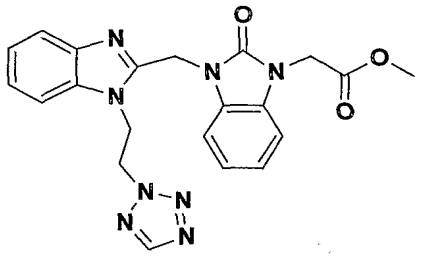
Compound 253



Compound **253** was prepared as described for compound **252** using tetrazole instead of pyrazole.

^{1}H NMR (DMSO-d6) δ 1.21 (t, J = 7.1Hz, 3H), 2.09 (s, 2H), 4.15 (q, J = 7.1Hz, 2H), 4.77 (s, 2H), 5.00-5.03 (m, 1H), 5.19-5.22 (m, 3H), 7.04-7.07 (m, 1H), 7.13-7.16 (m, 1H), 7.18-7.23 (m, 2H), 7.51-7.65 (m, 3H), 8.91 (s, 1H);
MS (m/e) 447 (MH^+).

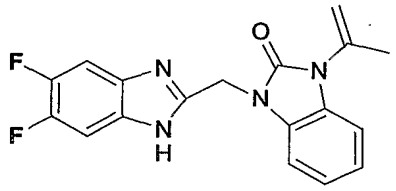
Compound 254



Compound **254** was prepared by transesterification using NaOMe as previously described for compound **131**.

^{1}H NMR (DMSO-d6) δ 3.34 (bs, 2H), 4.08 (s, 2H), 4.86 (bs, 2H), 5.26 (s, 2H), 6.93-7.02 (m, 3H), 7.14-7.24 (m, 3H), 7.24-7.31 (m, 1H), 7.61-7.63 (m, 1H), 9.33 (s, 1H);
MS (m/e) 431 (MH^+).

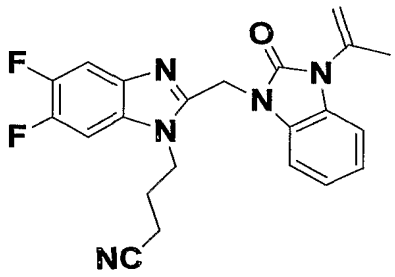
Compound 255 (Scheme III)



A mixture of 6-amino-3,4-difluoroaniline (1.2g, 8.33 mmol, from Specs), acid **182** (2.13 g, 8.33 mmol), and EEDQ (2.06 g, 8.33 mmol) were stirred in THF (40 mL) at reflux for 12 h. The mixture was evaporated and the residue was purified by chromatography on silica gel to give 850 mg of compound **255**:

^{1}H NMR (CD_3OD) δ 2.26 (s, 3H), 5.28 (s, 1H), 5.37 (s, 2H), 5.49 (s, 1H), 7.03-7.24 (m, 4H), 7.37-7.43 (m, 2H);
IR (KBr, cm^{-1}) 1686, 1655, 1491, 1471, 1405, 1346, 1157, 883, 859, 634, 600;
MS m/e 339 (MH^+);
Anal. Calcd for $C_{18}H_{14}F_2N_4O$: C, 63.53; H,4.15; N, 16.46
Found: C, 63.28; H, 4.37; N, 16.21.

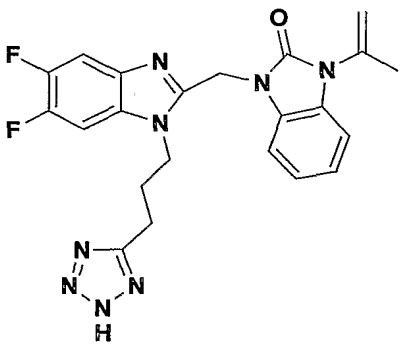
Compound 256



Compound **256** was prepared from **255** and 4-bromobutyronitrile in the same manner as compound **4.**

^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.92-2.02 (m, 2H), 2.25 (s, 3H), 2.47 (t, J = 7.3 Hz, 2H), 4.44-4.49 (m, 2H), 5.22 (s, 1H), 5.35 (s, 2H), 5.42 (s, 1H), 7.11-7.13 (m, 3H), 7.17 (dd, J = 6.7, 9.5 Hz, 1H), 7.49-7.53 (m, 1H), 7.58 (dd, J = 7.2, 10.2 Hz, 1H);
IR (KBr, cm^{-1}) 1686, 1487,1471, 1401, 1155, 753;
MS m/e 408 (MH^+);
Anal. Calcd for $C_{22}H_{19}F_2N_5O$ .0.25 H_2O C, 64.14; H,4.77; N, 17.00
Found: C, 64.03; H, 4.97; N, 17.18.

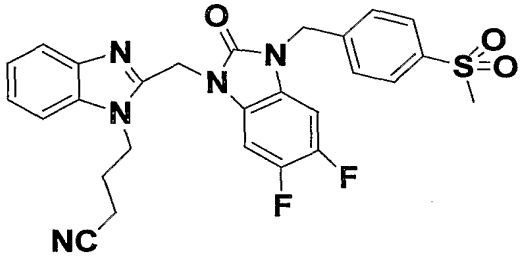
Compound 257



Compound **257** was prepared in the same manner as compound **52**.

^{1}H NMR (CD_3OD) δ 2.13-2.23 (m, 2H), 2.21 (s, 3H), 2.94 (t, J = 7.6 Hz, 2H), 4.44 (t, J = 7.6 Hz, 2H), 5.37 (s, 1H), 5.43 (s, 2H), 5.45 (s, 1H), 7.06-7.23 (m, 4H), 7.41-7.52 (m, 2H);
IR (KBr, cm^{-1}) 3411, 1698, 1681, 1654, 1487, 1470, 1407, 1157, 753;
MS m/e 451 (MH^+).

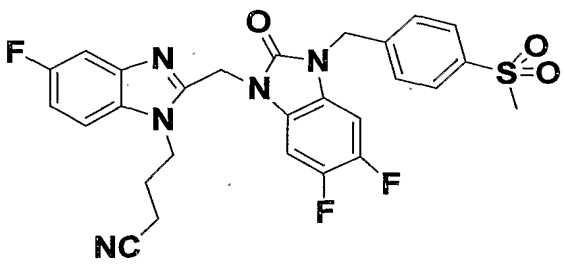
Compound 258



Compound **258** was prepared as described for compound **105**.

^{1}H NMR (DMSO-d6) δ 2.07-2.13 (m, 2H), 2.63 (t, J = 7.4Hz, 2H), 3.20 (s, 3H), 4.42 (t, J= 7.4Hz, 2H), 5.24 (s, 2H), 5.46 (s, 2H), 7.19 (t, J = 7.5Hz, 1H), 7.27 (t, J = 7.5Hz, 1H), 7.50-7.54 (m, 1H), 7.56 (d, J = 7.8Hz, 1H), 7.61 (d, J = 8.3Hz, 2H), 7.92 (d, J = 8.3Hz, 2H);
MS m/e 535 (MH^+).

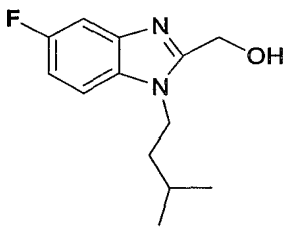
Compound 259



Compound **259** was prepared described for compound **105.**

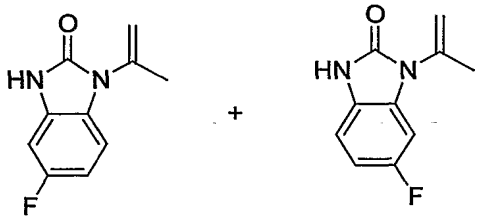
^{1}H NMR (DMSO-d6) δ 2.07-2.15 (m, 2H), 2.64 (t, J = 7.5Hz, 2H), 3.20 (s, 3H), 4.42 (t, J = 7.5Hz, 2H), 5.23 (s, 2H), 5.45 (s, 2H), 7.15 (td, J = 2.5, 9.3Hz, 1H), 7.40 (dd, 2.4, 9.8Hz, 1H), 7.45-7.53 (m, 2H), 7.60 (d, J = 8.3Hz, 2H), 7.63-7.65 (m, 1H), 7.92 (d, J = 8.3Hz, 2H);
MS m/e 553 (MH^+).

Compound 260



Compound **260** was prepared as described for compound **266.**

Compounds 261 and 262



261 **262**

A mixture of 3-fluorobenzenediamine (6.3 g, 50.0 mmol) and ethyl acetoacetate (6.50 g, 50.0 mmol) and DBU (0.76 g, 5.0 mmol) in p-xylene (50 mL) was heated to reflux for 2 h. Water formed during reaction was removed with a Dean-Stark trap. After cooling, the solvent was removed in vacuo. The residue was purified by flash chromatography (gradient, hexanes:EtOAc 4:1 to 1:1) to give 0.76 mg (8%) of 5-fluoro-1-isopropenyl-1,3-dihydro-benzoimidazol-2-one, **261** and 1.10 (11%) of 6-fluoro-1-isopropenyl-1,3-dihydro-benzoimidazol-2-one **262** as white solids.

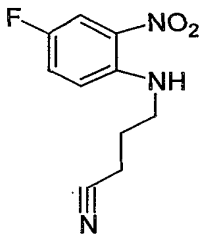
261: 5-Fluoro-1-isopropenyl-1,3-dihydro-benzoimidazol-2-one

^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 5.24 (d, J = 0.4 Hz, 1H), 5.41-5.43 (m, 1H), 6.77-6.81 (m, 1H), 6.89-6.91 (m, 1H), 6.98-7.00 (m, 1H);
MS m/e 193 (MH^+);

262: 6-Fluoro-1-isopropenyl-1,3-dihydro-benzoimidazol-2-one

^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 5.24 (s, 1H), 5.42 (d, J = 1.2 Hz, 1H), 6.78-6.85 (m, 2H), 7.03-7.06 (m, 1H);
MS m/e 193 (MH^+).

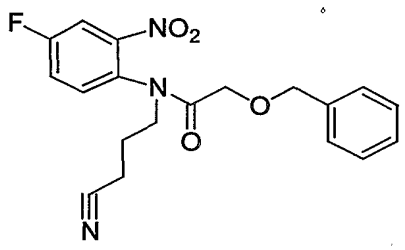
Compound 263



A solution of 2,5-difluoronitrobenzene (15.4 g, 96.8 mmol), 4-aminobutyronitrile (7.4 g, 88 mmol) and diisopropylethylamine (23 ml, 132 mmol) in DMF (250 ml) was stirred at room temperature for 32 hours. After filtration, the solvent was evaporated and the orange solid was recrystallized from MeOH (250 ml) to afford **263** (14 g, 65% yield) as orange crystals.

^{1}H NMR ($CDCl_3$) δ 2.06-2.12 (m, 2H), 2.54 (t, J = 7.0 Hz, 2H), 3.48-3.53 (m, 2H), 6.85-6.88 (m, 1H), 7.27-7.31 (m, 1H), 7.89-7.92 (m, 1H);
MS m/e 224 (MH^+).

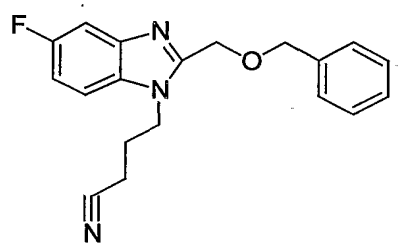
Compound 264



To a suspension of nitrile **263** (10.8 g, 48.4 mmol) and potassium carbonate (20.1 g, 145 mmol) in CH_3CN (200 ml) was added benzyloxyacetyl chloride (7.64 ml, 48.4 mmol) dropwise. After stirring at room temperature for 12 hours, the mixture was diluted with EtOAc (500 ml) and filtered. The filtrate was washed with 1 N HCl, brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 1:1) to yield **264** (7.5 g, 42% yield) as a viscous pale yellow oil.

^1H NMR ($CDCl_3$) δ 1.86-1.98 (m, 2H), 2.38-2.51 (m, 2H), 3.34-3.39 (m, 1H), 3.80-3.87 (m, 2H), 4.06-4.14 (m, 1H), 4.40-4.48 (m, 2H), 7.18-7.19 (m, 1H), 7.26-7.40 (m, 5H), 7.72-7.74 (m, 1H);
MS m/e 394 (MH^+).

Compound 265

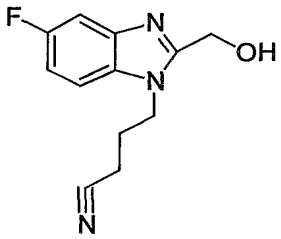


In a flask equipped with a mechanical stirrer, a suspension of compound **264** (6.40 g, 17.25 mmol), iron powder (2.89 g, 51.8 mmol) and ammonium chloride (4.61 g, 86.2 mmol) in a mixture of MeOH and H_2O (200 ml, 1:1) was stirred at reflux for 4 hours. The mixture was filtered through a pad of Celite and washed with MeOH. The filtrate was evaporated and the residue was taken up in EtOAc (500 ml), washed with brine, dried over $MgSO_4$, and evaporated. To the residue was added CH_3CN (100 ml) and acetic acid (1 ml), and the mixture was stirred at reflux for 4

hours. The solvent was evaporated and the residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 2:1) to give **265** (4.42 g, 75% yield) as a viscous oil which solidified upon standing.

^{1}H NMR ($CDCl_3$) δ 2.15-2.20 (m, 2H), 2.31 (t, J = 7.0 Hz, 2H), 4.35 (t, J = 7.2 Hz, 2H), 4.62 (s, 2H), 4.83 (s, 2H), 7.07-7.11 (m, 1H), 7.29-7.38 (m, 6H), 7.43-7.46 (dd, J = 2.4, 9.2 Hz, 1H);
MS m/e 324 (MH^+).

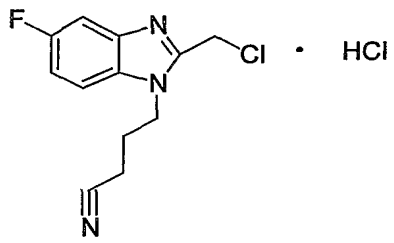
Compound 266



To a solution of **265** (3.23 g, 10 mmol) in CH_2Cl_2 (100 ml) at 0 ^{0}C was added boron tribromide (2.84 ml, 30 mmol). After stirring for 1 hour, the mixture was quenched with saturated $NaHCO_3$ solution with ice bath cooling and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) to give **266** (1.68 g, 72% yield) as an off-white solid.

^{1}H NMR ($CDCl_3$) δ 2.25-2.30 (m, 2H), 2.43 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 7.1 Hz, 2H), 4.85 (s, 2H), 7.04-7.081 (m, 1H), 7.29-7.34 (m, 2H);
MS m/e 234 (MH^+).

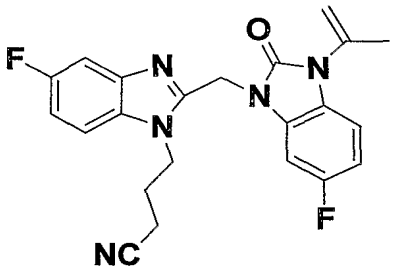
Compound 267



Compound **267** was prepared according to the same procedure described for compound **6**.

^{1}H NMR (CD_3OD) δ 2.30-2.36 (m, 2H), 2.70 (t, J = 7.2 Hz, 2H), 4.67 (t, J = 7.6 Hz, 2H), 5.30 (s, 2H), 7.49-7.54 (dt, J = 2.4, 9.2 Hz, 1H), 7.62-7.64 (dd, J = 2.4, 8.0 Hz, 1H), 8.01-8.04 (dd, J = 2.0, 9.2 Hz, 1H);
MS m/e 252 (MH^+).

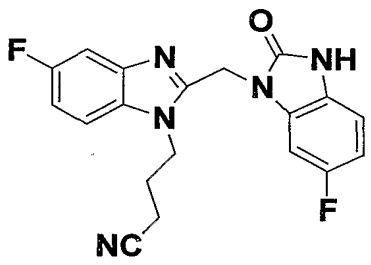
Compound 268



Compound **268** was prepared as described for compound **106** using intermediates **267** and **261**.

^{1}H NMR ($CDCl_3$) δ1.90-1.95 (m, 2H), 2.16 (s, 3H), 2.37-2.40 (m, 2H), 4.43 (t, J = 7.6Hz, 2H), 5.12 (s, 1H), 5.26 (s, 2H), 5.33 (s, 1H), 6.71-6.75 (m, 1H), 6.92-6.95 (m, 1H), 7.00-7.04 (m, 1H), 7.22-7.40 (m, 2H), 7.40-7.42 (m, 1H).

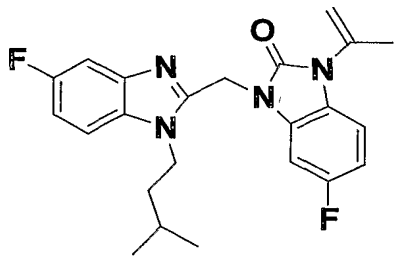
Compound 269



Prepared from compound **268** as described for compound **6**.

^{1}H NMR (DMSO-d6) δ 2.09-2.16 (m, 2H), 2.67 (t, J = 7.5Hz, 2H), 4.51 (t, J = 7.5Hz, 2H), 5.50 (s, 2H), 6.84-6.88 (m, 1H), 7.01-7.04 (m, 1H), 7.21-7.23 (m, 1H), 7.30-7.34 (m, 1H), 7.49-7.52 (m, 1H), 7.83-7.86 (m, 1H);
MS m/e 368 (MH^+).

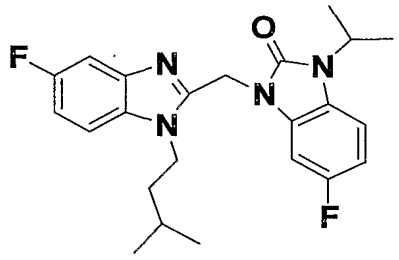
Compound 270



Compound **270** was prepared as described for compound **106** using **262** and **267**.

^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.42-1.46 (m, 2H), 1.67-1.71 (m, 1H), 2.23 (s, 3H), 4.29-4.32 (m, 2H), 5.19 (s, 1H), 5.34 (s, 2H), 5.39 (s, 1H), 6.75-6.85 (m, 2H), 7.02-7.07 (m, 1H), 7.21-7.24 (m, 1H), 7.36-7.46 (m, 2H);
MS m/e 411 (MH+).

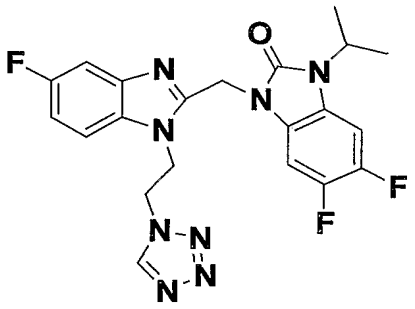
Compound 271



Compound **271** was prepared from compound **270** as described for compound **115**.

^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.6 Hz, 6H), 1.41-1.45 (m, 2H), 1.53 (d, J = 7.0 Hz, 6H), 1.66-1.72 (m, 1H), 4.28-4.31 (m, 2H), 4.70-4.74 (m, 1H), 5.32 (s, 2H), 6.72-6.76 (m, 1H), 6.85-6.87 (m, 1H), 7.02-7.06 (m, 1H), 7.20-7.23 (m, 1H), 7.34-7.36 (m, 1H), 7.43-7.46 (m, 1H);
MS m/e 411 (MH^+).

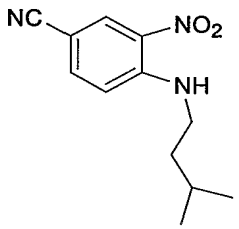
Compound 272



Compound **272** was prepared as described for compound **115**.

^{1}H NMR (DMSO-d6) δ 1.45 (d, J = 5.2Hz, 6H), 3.21-3.33 (m, 2H), 4.51-4.71 (m, 2H), 4.81-5.10 (m, 4H), 5.41 (s, 2H), 6.91-7.15 (m, 1H), 7.21-7.51 (m, 3H), 7.52-7.62 (m, 1H), 9.30 (s, 1H);
MS m/e 456 (MH^+).

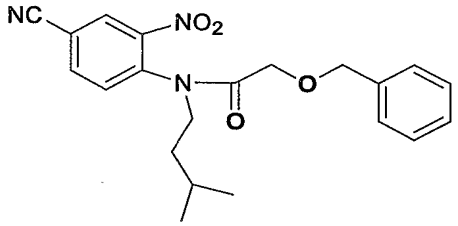
Compound 273



Compound **273** was prepared by addition of 3-methyl-butylamine to 3-chloro-4-nitro benzonitrile as described for compound **233.**

^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 6.5 Hz, 6H), 1.63-1.70 (m, 2H), 1.74-1.83 (m, 1H), 3.34-3.41 (m, 2H), 6.93 (d, J = 9.0 Hz, 1H), 7.62 (dd, J = 1.9, 8.9 Hz, 1H), 8.35-8.40 (m, 1H), 8.53 (d, J = 2.0 Hz, 1H);
MS m/e 321 ($M^+NH_4^+$).
Calcd for $C_{12}H_{15}N_3O_2$: C 61.69; H 6.48; N 18.01;
Found: C 61.75; H 6.39; N 17.94.

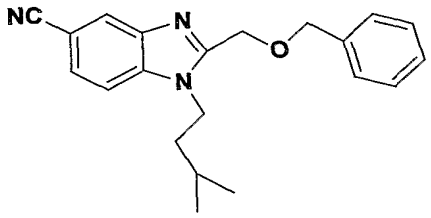
Compound 274



To a mixture of compound **273** (10.8 g, 48.4 mmol) and K_2CO_3 (20.1 g, 145 mmol) in CH_3CN (200 ml) was added benzyloxyacetic chloride and stirred for 12 h. Diluted with EtOAc, filtered. The filtrate was washed with $NaHCO_3$ and brine, dried, evaporated. The residue was recrystallized from MeOH to yield 7.5 g (42%) of compound **274** as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.58 (q, J = 6.8 Hz, 2H), 1.66-1.77 (m, 1H), 2.26 (s, 3H), 3.18 (t, J = 7.3 Hz, 2H), 4.73 (s, 2H), 6.76-6.78 (m, 1H), 7.46-7.53 (m, 3H);
MS m/e 315 (MH^+).
Anal. Calcd for $C_{21}H_{25}N_3O_2$ C: 63.35; H 6.98; N 13.85.
Found: C, 63.37; H 6.87; N 13.72.

Compound 274a

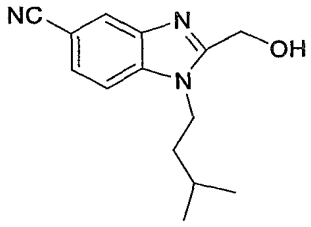


A mixture of compound **274** (6.4 g, 17.2 mmol), iron powder (2.89 g, 51.8 mmol) and ammonium chloride (4.61 g, 86.2 mmol) in MeOH (100 ml) and H_2O (100 ml) was heated to reflux for 4 h. The reaction mixture was filtered while hot through celite and the aqueous layer extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The residue was dissolved in CH_3CN (100 ml) and acetic acid (1 ml) and heated to reflux 4 h. The solvent was removed and the residue purified by flash chromatography eluting with hexanes-EtOAc (2:1 to 1:2) to yield 4.17 g (75%) of compound **274a** as a viscous oil.

1H NMR ($CDCl_3$) δ 1.86-1.98 (m, 2 H), 2.38-2.51 (m, 2 H), 3.34-3.39 (m, 1 H), 3.80-3.87 (m, 2 H), 4.06-4.14 (m, 1 H), 4.38-4.66 (m, 2 H), 7.18-7.19 (m, 1 H), 7.26-7.40 (m, 6 H), 7.72-7.74 (m, 1 H);

MS m/e 372 (MH^+).

Compound 275

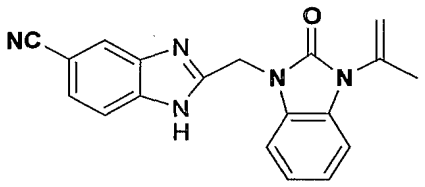


To a solution of compound **274a** (3.23 g, 10 mmol) in CH_2Cl_2 at 0°C was added BBr_3 (7.50 g, 30 mmol) and the reaction mixture stirred for 1 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and extraced with EtOAc. The organic layer was washed with brine, dried and evaporated. The residue was purified by flash chromatography eluting with CH_2Cl_2-MeOH (40:1 to 20:1) to yield 1.68 g (72%) of compound **275** as an off-white solid.

^1H NMR ($CDCl_3$) 2.25-2.31 (m, 2H), 2.43 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 7.1 Hz, 2H), 4.85 (s, 2H), 6.09 (b, 1H), 7.04-7.08 (m, 1H), 7.29-7.34 (m, 2H)

MS m/e 234 (MH^+).

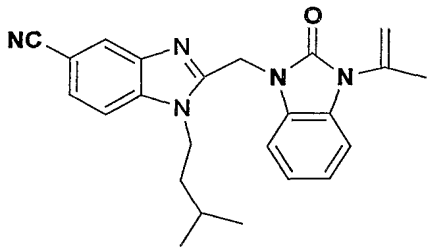
Compound 276



Compound **276** was prepared as described for compound **3**.

^{1}H NMR (DMSO-d6) δ 2.18 (s, 3H), 5.21 (s, 1H), 5.35 (s, 2H), 5.42 (d, J = 1.3Hz, 1H), 7.02-7.13 (m, 3H), 7.17-7.20 (m, 1H), 7.55-7.71 (m, 2H), 8.12 (bs, 1H), 13.08 (bs, 1H);
MS m/e 329 (MH^+).

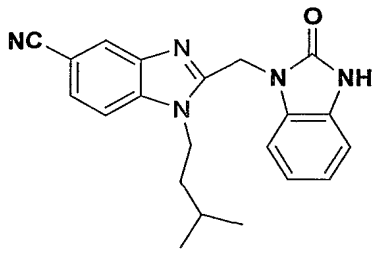
Compound 277



Compound **277** was prepared as described for compound **4**.

^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 6H), 1.41-1.49 (m, 2H), 1.67-1.76 (m, 1H), 2.23 (s, 3H), 4.43 (t, J = 8.1 Hz, 2H), 5.20 (s, 1H), 5.39 (s, J = 1.3 Hz, 1H), 5.50 (s, 2H), 7.09-7.10 (m, 3H), 7.43 (d, J = 8.5 Hz, 1H), 7.55-7.61 (m, 2H), 8.19 (s, 1H);
MS m/e 400 (MH^+).

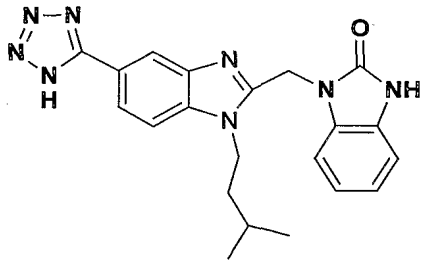
Compound 278



Compound **278** was prepared as described for compound **6**.

^{1}H NMR (CD_3OD) δ 1.21 (d, J = 6.6 Hz, 6H), 1.63-1.66 (m, 2H), 1.91-2.05 (m, 1H), 4.45 (t, J = 8.3 Hz, 2H), 5.70 (s, 2H), 7.28-7.39 (m, 4H), 7.88-7.90 (m, 2H), 8.29 (s, 1H);
MS m/e 360 (MH^+).

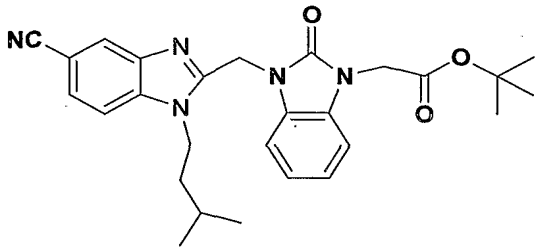
Compound 279



Compound **279** was prepared as described for compound **52**.

^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 6.6 Hz, 6H), 1.35-1.43 (m, 2H), 1.63-1.72 (m, 1H), 4.35 (t, J = 8.0 Hz, 2H), 5.37 (s, 2H), 6.91-7.03 (m, 3H), 7.12-7.15 (m, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.95 (dd, J = 1.6, 8.5 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 11.11 (s, 1H);
MS m/e 403 (MH^+).

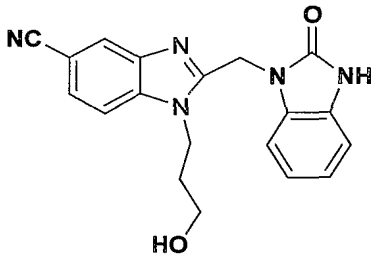
Compound 280



Compound **280** was prepared as described for compound **7** using tert-butylbromoacetate.

^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.45-1.57 (m, 2H), 1.48 (s, 9H), 1.68-1.77 (m, 1H), 4.34 (t, J = 8.3 Hz, 2H), 5.43 (s, 2H), 6.86-6.89 (m, 1H), 7.04-7.12 (m, 2H), 7.36-7.39 (m, 2H), 7.54 (dd, J = 1.2, 8.4 Hz, 1H), 8.13 (s, 1H);
MS m/e 474 (MH^+).

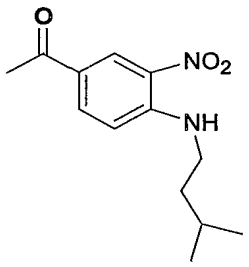
Compound 281



Compound **281** was prepared as described for **6.**

^{1}H NMR ($CDCl_3$) δ 2.07-2.14 (m, 2H), 4.43 (t, J = 6.1Hz, 2H), 4.55 (t, J = 7.6Hz, 2H), 5.41 (s, 2H), 7.05-7.14 (m, 3H), 7.38-7.45 (m, 2H), 7.58 (dd, J = 1.4, 8.4Hz, 1H), 8.00 (s, 1H), 8.15 (d, J = 5.4Hz, 1H);
MS m/e 347 (MH^+).

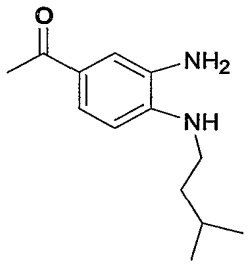
Compound 282



4-chloro-3-nitroacetophenone was treated with 3-methylbutyl amine to give 1-[4-(3-methyl-butylamino)-3-nitro-phenyl]-ethanone, compound **282**.

^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.6 Hz, 6H), 1.37-1.67 (m, 2H), 1.72-1.83 (m, 1H), 2.55 (s, 3H), 3.36-3.42 (m, 2H), 6.90 (d, J = 9.3 Hz, 1H), 8.07 (dq, J = 0.6, 9.3 Hz, 1H), 8.39-8.44 (s, 1H), 8.79 (d, J = 2Hz, 1H);
MS m/e 250 (MH^+).

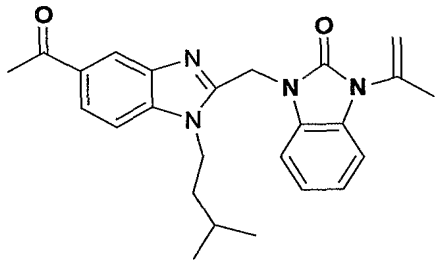
Compound 283



1-[4-(3-methyl-butylamino)-3-nitro-phenyl]-ethanone was reduced with catalytic hydrogenation as previously described for compound **164**.

^{1}H NMR ($CDCl_3$) d 0.97 (d, J = 6.6 Hz, 6H), 1.58 (q, J =7.2 Hz, 2H), 1.73-1.78 (m, 1H), 2.50 (s, 3H), 3.20 (t, J = 7.5 Hz, 2H), 6.58 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.52 (dd, J = 1.8, 8.2 Hz, 1H);
MS m/e 220 (MH^+).

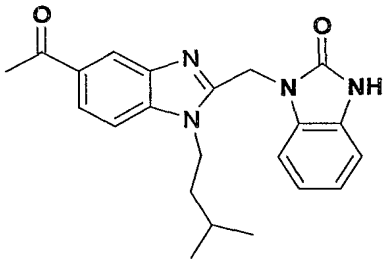
Compound 284



1-[3-Amino-4-(3-methyl-butylamino)-phenyl]-ethanone was coupled with compound **182** to give the final product using EEDQ as shown in Scheme IV.

^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 6H), 1.42-1.50 (m, 2H), 1.65-1.76 (m, 1H), 2.69 (s, 3H), 4.35-4.40 (m, 2H), 5.22 (s, 1H), 5.40 (d, J = 1.4 Hz, 1H), 5.43 (s, 2H), 7.05-7.12 (m, 3H), 7.36 (d, J = 8.6 Hz, 1H), 7.45-7.48 (m, 1H), 7.99 (dd, J = 1.5, 8.6 Hz, 1H), 8.43 (s, 1H);
MS m/e 417 (MH^+).

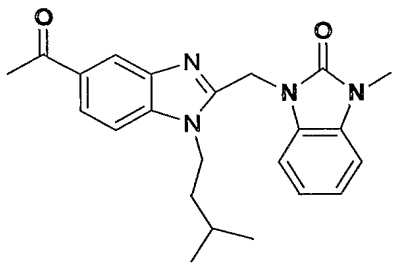
Compound 285



Compound **285** was prepared as previously described for compound **6**.

^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 6.6 Hz, 6H), 1.36-1.44 (m, 2H), 1.62-1.70 (m, 1H), 2.61 (s, 3H), 4.34 (t, J = 8.1 Hz, 2H), 5.37 (s, 2H), 6.91-7.03 (m, 3H), 7.10-7.14 (m, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.86 (dd, J = 1.6, 8.5 Hz, 1H), 8.29 (d, J = 1.0 Hz, 1H), 11.09 (s, 1H);
MS m/e 377 (MH+).

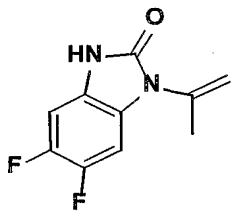
Compound 286



Compound **286** was alkylated with methyl iodide with sodium hydride as base as described for compound **7**.

^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 6H), 1.34-1.42 (m, 2H), 1.66-1.75 (m, 1H), 2.68 (s, 3H), 3.47 (s, 3H), 4.31-4.37 (m, 2H), 5.43 (s, 2H), 6.92-7.14 (m, 3H), 7.35 (d, J = 8.6 Hz, 1H), 7.38-7.41 (m, 1H), 7.98 (dd, J = 1.5, 8.6 Hz, 1H), 8.42 (d, J = 1.3 Hz, 1H);
MS m/e 391 (MH^+).

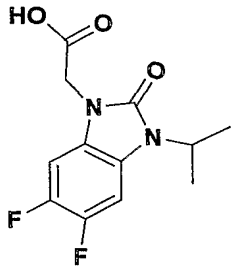
Compound 287



Compound **287** was prepared using the procedure of J. Davoll, J. Chem. Soc. 1960, p 308) using 2-amino-4,5-difluoroaniline.

^{1}H NMR (DMSO-d6) δ 2.21 (s, 3H), 5.20 (s, 1H), 5.36 (s, 1H), 7.03-7.12 (m, 2H).

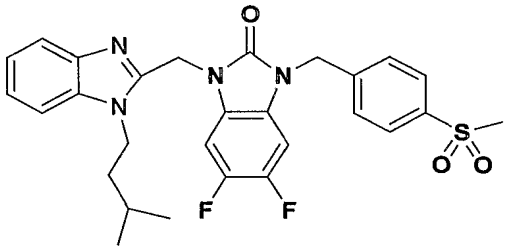
(5,6-Difluoro-3-isopropyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid



Compound **287** was alkylated with methyl bromo acetate as described for compound **181.** The isopropenyl group was reduced as described for compound **155** and the ester hydrolyzed as described for compound **182.**

^{1}H NMR $CDCl_3$: 1.52 (d, J = 7.0 Hz, 6H), 4.61 (s, 2H), 4.60-4.71 (m, 1H), 6.79-6.85 (m, 1H), 6.99-7.04 (m, 1H).

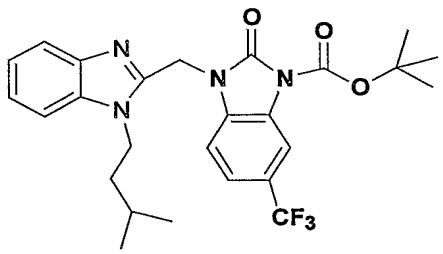
Compound 288



Compound **288** was prepared using the procedure shown in Scheme IV.

^{1}H NMR (DMSO-d_6) δ 0.93 (d, J = 6.6 Hz, 6H), 1.52-1.57 (m, 2H), 1.64-1.69 (m, 1H), 3.19 (s, 3H), 4.32 (t, J = 7.8 Hz, 2H), 5.23 (s, 2H), 5.43 (s, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.46-7.50 (m, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.58-7.62 (m, 4H), 7.91 (d, J = 8.2 Hz, 2H);
MS m/e 538 (MH^+).

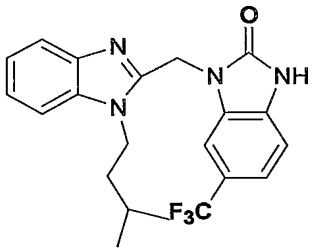
Compound 289



Prepared from compound **107** and 2-oxo-6-trifluoromethyl-2,3-dihydro-benzoimidazole-1-carboxylic acid tert-butyl ester [mixture of 5 and 6 regioisomers 2-oxo-trifluoromethyl-2,3-dihydro-benzoimidazole (Meanwell et al. *J. Org. Chem.* **1995**, *60*, 1565-1582) were separated by column chromatography and alkylated with methyl bromoacetate] as previously described for compound **108**.

^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, 6H), 1.36-1.43 (m, 2H), 1.61 (s, 9H), 1.64-1.73 (m, 1H), 4.23-4.29 (m, 2H), 5.32 (s, 2H), 7.19-7.25 (m, 4H), 7.31-7.34 (m, 1H), 7.70-7.76 (m, 2H), 7.82 (d, J = 8.5 Hz, 1H);
MS m/e 503 (MH+).

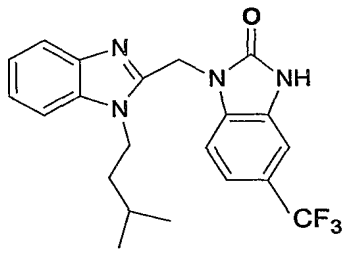
Compound 290



The t-butylcarbamate was removed as previously described for compound **6**.

^{1}H NMR (CD_3OD) δ 0.96 (d, J = 6.6 Hz, 6H), 1.39-1.47 (m, 2H), 1.67-1.75 (m, 1H), 4.35 (t, J = 8.3 Hz, 2H), 5.44 (s, 2H), 7.19-7.38 (m, 4H), 7.45-7.47 (m, 2H), 7.46 (d, J = 7.3 Hz, 1H);
MS m/e 403 (MH+).

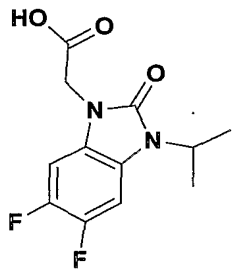
Compound 291



Compound **291** was prepared in a similar manner as for compound **290** above.

^{1}H NMR (DMSO-d_6) δ 0.92 (d, J = 6.6 Hz, 6H), 1.39-1.46 (m, 2H), 1.61-1.70 (m, 1H), 4.29 (t, J = 8.1 Hz, 2H), 5.37 (s, 2H), 7.05-7.25 (m, 3H), 7.29-7.36 (m, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 11.44 (s, 1H).

(5,6-Difluoro-3-isopropyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid



(5,6-Difluoro-3-isopropyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid was prepared by hydrogenation of (5,6-Difluoro-3-isopropenyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-acetic acid as described for compound **115** then alkylated as described for compound **181** and hydrolysis to the acid as described for **182**.

^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 7.0 Hz, 6H), 4.61 (s, 2H), 4.60-4.71 (m, 1H), 6.79-6.85 (m, 1H), 6.99-7.04 (m, 1H).

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at 1.5x10^4 cells/100 μL/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10%

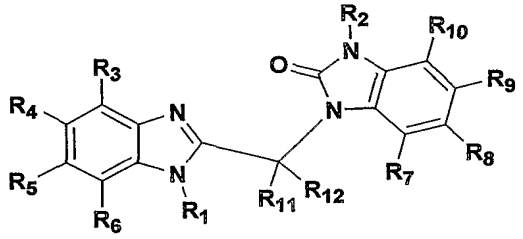
fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μL volume in medium containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μL at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethlythiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was aspirated from the cells and 100 μL/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μg/mL (corresponding to 10.2 μM).

The antiviral activity of compounds, designated as EC_{50}, is presented as a concentration that produces 50% cell protection in the assay. The compounds disclosed in this application show antiviral activity with EC_{50}s between 50 μM and 0.001 μM. Ribavirin has an EC_{50} of 3 μM in this assay.

CLAIMS

What is claimed is:

1. A compound having the Formula I, and pharmaceutically acceptable salts thereof,



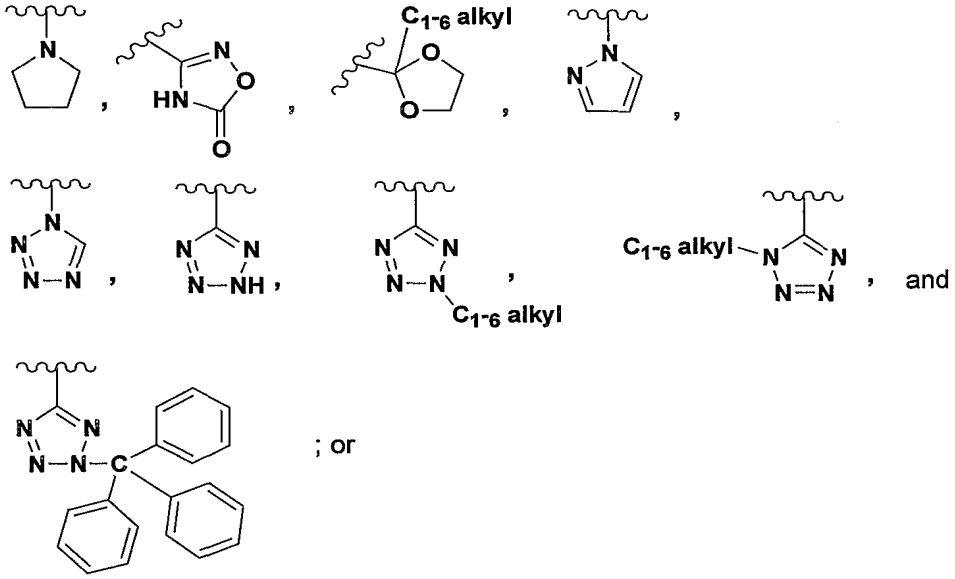
Formula I

wherein:

R_1 is $-(CR^vR^w)_n-X$;

R^v and R^w are independently selected from the group consisting of H, C_{1-6} alkyl, and C_{2-6} alkenyl; optionally substituted with 1-6 of the same or different halogen;

X is H, C_{1-6} alkyl, C_{2-6} alkenyl; each of said C_{1-6} alkyl, C_{2-6} alkenyl being optionally substituted with (1) one to six same or different halogen or hydroxy; (2) a member selected from the group consisting of phenyl, $-C(=NOH)NH_2$, $-CH(OH)-Ph$, $-Ph-S(O)_2C_{1-6}$ alkyl,



; or

(3) a member from Group A1;

Group A1 is CN, OR', NR'R", R'NCOR", NR'CONR"R'", NR'SO_2R", NR'COOR", COR', COOR', $OS(O)_2$R', $S(O)_t$R' or $PO(OR')_2$;

n is 1-6;

t is 0-2;

R_2 is

(i) H, C_{1-6} alkyl, C_{2-6} alkenyl, phenyl, or a functionality selected from Group A2 or Group B; each of said C_{1-6} alkyl, C_{2-6} alkenyl, and phenyl being optionally substituted with (1) one to six same or different halogen or hydroxy or (2) one to two same or different members of Group A or Group B;

(ii) $-(CR^xR^y)_{n'}-(CO)_p-C_6H_4-(Z_1)(Z_2)$, wherein Z_1 and Z_2 are each independently selected from the group consisting of Group A, Group B, and $-(CH_2)_{n'}-Z'$; wherein said Z' is heterocycle or $-(NR_dR_eR_f)$ + (halogen)-; and the Z_1 and Z_2 groups may each be in the ortho, meta or para position relative to the $-(CR^xR^y)_{n'}-(CO)_p-$ group; wherein R_d, R_e and R_f are independently C_{1-6} alkyl, C_{2-6} alkenyl, OH or C_{1-6} alkyl COOH;

p is 0 or 1;

n' is 1-6; or

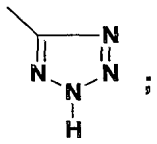
(iii) $-(CR^xR^y)_{n''}$-heterocycle;

n" is 0-6;

R_3, R_6, R_7 and R_{10} are each independently H;

R_5, R_8 and R_9 are each independently H, halogen or CF_3;

R_4 is selected from the group consisting of H, halogen, CN, $-C(O)C_{1-6}$ alkyl and



;

R_{11}, R_{12} are each independently H;

R^x, R^y are each independently H or C_{1-6} alkyl;

Group A2 is COR', COOR', CONR'R" or CONR'SO_2R";

Group A3 is CN, NO_2, OR', OCONR'R", NR'R", N(R') COR", N(R')CONR"R'", NR'SO_2R", NR'COOR", SO_mR', SO_2NR'R", SO_2NR'COR" or $PO(OR')_2$;

Group A is a member selected from Group A2 and Group A3;

R', R", R'" are each independently selected from the group consisting of H, C_{1-6} alkyl, phenyl and heterocycle; and each of said C_{1-6} alkyl, phenyl and heterocycle being optionally substituted with (1) one to six of same or different halogen or hydroxy; (2) one to two of the same or different members of Group A' or Group B; or (3) heterocycle; or R' and R" taken together form a 5 to 6 membered aromatic or non-aromatic ring containing one to four of the same or different heteroatoms selected from the group consisting of N, S and O;

Group A' is halogen, CN, NO_2, OR^a, $OCONR^aR^b$, NR^aR^b, R^aNCOR^b, $NR^aCONR^bR^c$, $NR^aSO_2R^b$, NR^aCOOR^b, COR', $CR^cNNR^aR^b$, CR^aNOR^b, $COOR^a$, $CONR^aR^b$, $CONR^aSO_2R^b$, $SO_{m'}R^a$, $SO_2NR^aR^b$, $SO_2NR^aCOR^b$ or $PO(OR^a)_2$;

R^a, R^b, R^c are each independently selected from the group consisting of H and C_{1-6} alkyl;

Group B is $-(CH_2)_{n'''}Q$, $-(CH_2)_{n'''}SO_{m''}-R_{13}$ or -COQ;

Q is an N-linked amino acid selected from the group consisting of alanine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, pipecolic acid, α-amino-butyric acid, α-amino-propanoic acid, 2-amino-3-phonopropionic acid and iminodiacetic acid; wherein Q is linked to the adjacent carbon atom in Group B through a nitrogen atom of said N-linked amino acid; wherein said N-linked amino acid includes D- or L-enantiomers or mixtures thereof;

R_{13} is selected from a group consisting of H and C_{1-6} alkyl; said C_{1-6} alkyl being optionally substituted with (1) one to five hydroxy groups or (2) two of the same or different functionalities selected from the group consisting of $COOR^x$ and $CONR^xR^y$;

m, m' and m'' are independently 0-2;

n''' is 1-6;

heterocycle is a 5-6 membered aromatic or non-aromatic ring which contains one to four heteroatoms independently selected from the group consisting of O, N and S; wherein said aromatic or non-aromatic ring is optionally fused to a phenyl ring; wherein the aromatic or non-aromatic ring is optionally substituted with one to five of the same or different substituents selected from the group consisting of C_{1-6} alkyl, Group A and Group B; and halogen is bromine, chlorine, fluorine or iodine.

2. A compound of claim 1 wherein heterocyle is an aromatic ring selected from the group consisting of furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl,

pyrazinyl, 1,3,5-triazinyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, tetrazole, uridinyl and cytosinyl.

3. A compound of claim 1 wherein the heterocyle is a non-aromatic ring selected from the group consisting of pyrrolidine, imidazoline, 2-imidazolidone, 2-pyrrolidone, pyrrolin-2-one, tetrahydrofuran, 1,3-dioxolane, piperidine, tetrahydropyran, oxazoline, 1,3-dioxane, 1,4-piperazine, morpholine and thiomorpholine.

4. A compound of claim 1 wherein:

R_1 is $-(CH_2)_n-X$.

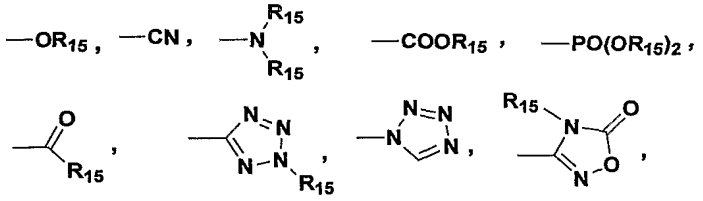
5. A compound of claim 1 wherein in R_2, substituents R^x and R^y are each hydrogen.

6. A compound of claim 1 wherein in R_1, n is 1-4.

7. A compound of claim 5 wherein in R_2, n' is 1; and n" is 3-4.

8. A compound of claim 1 wherein:

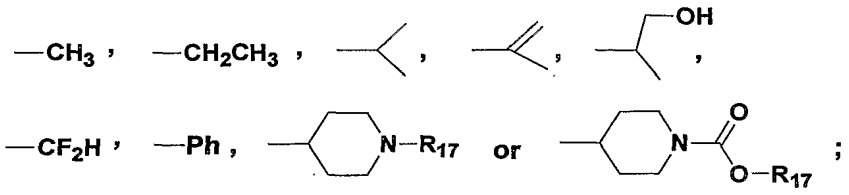
R_1 is vinyl, allyl, 3-methyl-2-butene or -(CH$_2$)n-X, wherein n is 2-4, and X is a functionality selected from the group consisting of



$-NHCOR_{15}$, $-NHSO_2R_{15}$, $-SR_{15}$ and $-SO_2R_{15}$;

R_2 is

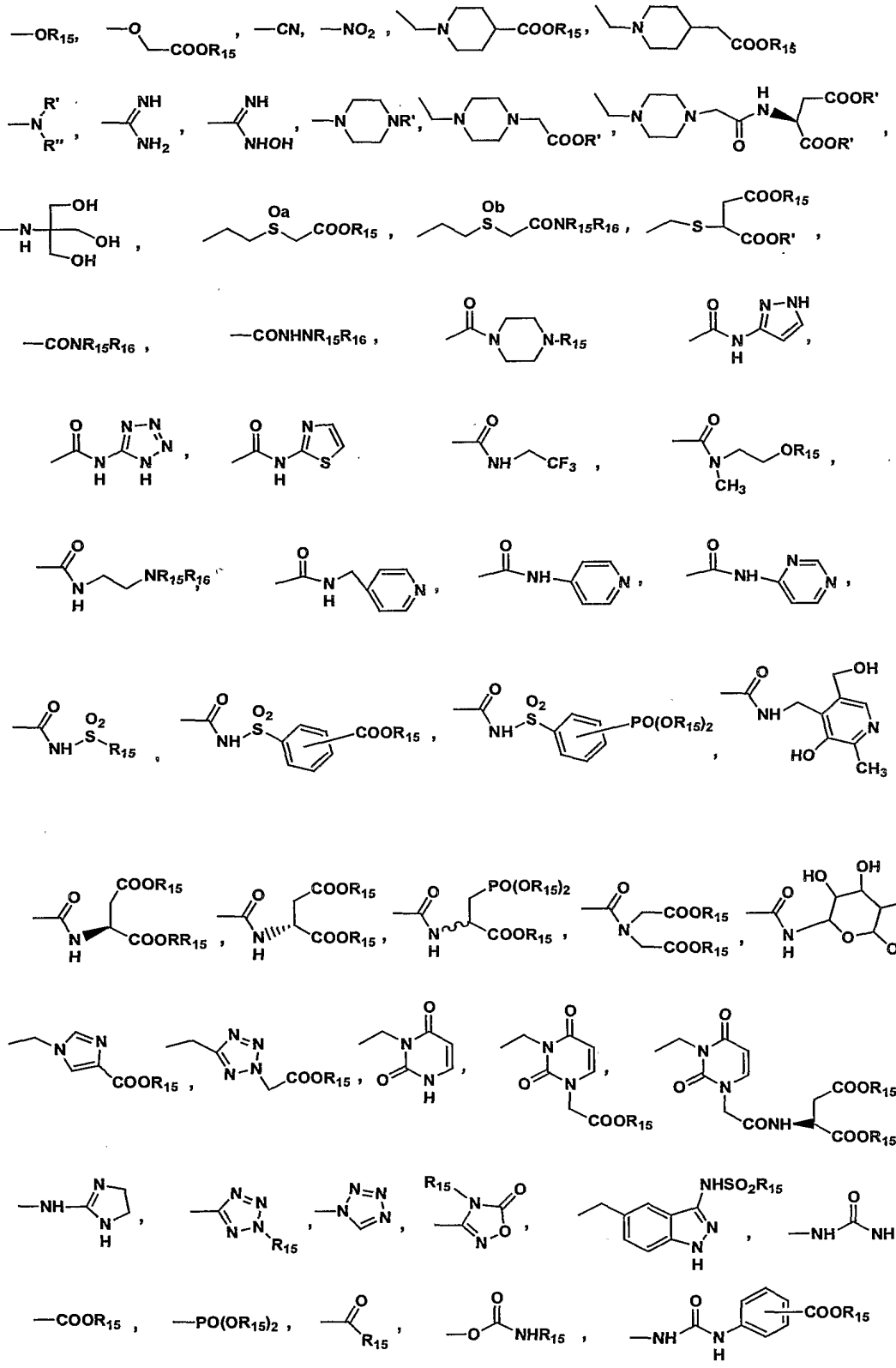
(i)



wherein R_{17} is H or C_{1-4} alkyl;

(ii) $-CH_2-C_6H_4-Z$;

(iii) $-(CH_2)_k-Z''$, wherein k is 1-6; wherein Z and Z'' are each independently selected from the group consisting of:



—NHCOR15 , —NHSO2R15 , —NHSO2CF3 , —SR15 , —SO2R15 , —SO2NR15R16 and —SO3H ;

and b are each independently 0-2; and

R_{15} and R_{16} are each independently H, C_{1-4} alkyl, wherein said C_{1-4} alkyl is optionally substituted with 1-3 same or different halogens.

9. A method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds as claimed in any one of claims 1-8.

10. A pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned anti-RSV compounds as claimed in any one of claims 1-8 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/29493

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MEANWELL et al. Regiospecific Functionalization of 1,3-Dihydro-2H-benzimidazol-2-one and Structurally Related Cyclic Urea Derivatives. J. Org. Chem. 24 March 1995, Vol. 60, No. 6, pages 1565-1582, especially page 1571, entry 75.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 27 NOVEMBER 2001	Date of mailing of the international search report 17 JAN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LAURA L. STOCKTON Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/29493

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 31/4184, 31/443, 31/422, 31/427, 31/454, 31/501, 31/5377; C07D 401/14, 403/06, 403/14, 413/14, 417/14

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/81, 234.5, 254.06, 274, 322, 338, 363, 364, 369, 376, 381, 387; 544/139, 310, 370; 546/199, 273.7; 548/113, 132, 139, 181, 250, 251, 252, 305.7

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/81, 234.5, 254.06, 274, 322, 338, 363, 364, 369, 376, 381, 387; 544/139, 310, 370; 546/199, 273.7; 548/113, 132, 139, 181, 250, 251, 252, 305.7